Chapter 4

Wearable Neuromodulators

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.76673

Abstract

In neuromodulation, by delivering a form of stimulus to neural tissue the response of an associated neural circuit may be changed, enhanced or inhibited (i.e., *modulated*) as desired. This powerful technique may be used to treat various medical conditions as outlined in this chapter. After a brief introduction to the human nervous system, key example applications of electrical neuromodulation such as cardiac pacemakers, devices for pain relief, deep brain stimulation, cochlear implant and visual prosthesis and their respective methods of deployment are discussed. Furthermore, key features of wearable neuromodulators with reference to some existing devices are briefly reviewed. This chapter is concluded by a case study on design and development of a wearable device with non-invasive electrodes for treating lower urinary tract dysfunctions after spinal cord injury.

Keywords: lower urinary tract, electrical stimulation, nervous system, neuromodulation, spinal cord injury, TENS, transcutaneous stimulation

1. Introduction

In neuromodulation by applying a form of stimulus to neural tissue, the response of the underlying neural circuits is modulated and a response is evoked. In this chapter, we solely focus on electrical stimulation of neural tissue. Neuromodulation is used to suppress pain, assist locomotion, treat various conditions and rehabilitate patients. Current neuromodulators are primarily used for medical purposes. Neuromodulators may be classified as invasive, where a form of surgical operation is required to implement the technique, or non-invasive, where surface electrodes are used. Due to the risks associated with surgery and high cost, non-invasive solutions are more desirable. Both classes of neuromodulators may be controlled by the user

or be completely autonomous and this depends on the application. Most of them are portable and may be on the person while they go about their daily life. Invasive neuromodulators may not be removed when desired. However, if they are composed of external and implanted units, the external part may be detached from the patient if needed. While connectivity can be readily incorporated in such devices, this is not at this stage a fundamental part of such solutions.

After an introduction to human nervous system, fundamentals of neuromodulation are described in this chapter. Key examples of neuromodulation devices are briefly discussed, followed by a note on wearable neuromodulators. This chapter is concluded by a discussion on the design and development of a wearable neuromodulator to treat lower urinary tract (LUT) dysfunctions after spinal cord injury (SCI).

2. Human nervous system

This section is a brief and general introduction to human nervous system, aiming to assist readers in understanding what follows in the chapter.

2.1. Central and peripheral systems

The human nervous system may be divided into central and peripheral systems. The central nervous system (CNS) comprises the brain and the spinal cord and the peripheral nervous system (PNS) mainly includes the nerves that connect the periphery of the body to the CNS. The brain comprises the cerebral hemispheres, diencephalon, cerebellum, and the brainstem. The spinal cord connects lower parts of the body to the brain and can be divided into four sections, each of which has various segments from top to bottom: cervical (C1–C8), thoracic (T1–T12), lumbar (L1–L5), and sacral (S1–S5) [1].

The PNS comprises the spinal nerves, originating from the spinal cord, and most of the cranial nerves, originating from the brain, above the spinal cord. The peripheral nerves originating from a specific segment of the spinal cord (C-S) generally mediate a specific functionality. The PNS may be subdivided into the autonomic nervous system and somatic nervous system. Generally, the former oversees the involuntary control and the latter provides the voluntary control. The autonomic nervous system may be further divided into sympathetic and parasympathetic nervous systems. The sympathetic nervous system may be perceived to oversee the fight-or-flight response while the parasympathetic nervous system is responsible for the rest-and-digest functions.

2.2. Key elements

There are two main classes of cells in the nervous system: nerve cells (neurons) and glial cells (glia). Generally, the former are the ones involved in neural signaling and the latter function as support cells. Typically, a neuron may consist of four distinct regions: a soma, dendrites, an axon, and presynaptic terminals [2]. The main function of neurons is to convey the neural signal (i.e., action potential (AP)).

Soma houses cell genes and proteins are synthesized in it. A soma may give rise to two types of projections, also referred to as processes. There may be one long axon, also referred to as the nerve fiber, which acts as the main conducting unit of the neural signal (i.e., AP) to other neurons. Other projections, which are generally shorter and branch-like, are dendrites. Dendrites may be thought of as the main neural signal receiving ports in a neuron. Near the end, an axon divides into these branches which communicate with other neurons through the presynaptic terminals. The point of communication between a neuron and other neurons is called a synapse. The cell transmitting the signal is called a presynaptic cell and the one receiving it is called the postsynaptic cell. Presynaptic terminals land on the soma and/or the dendrites of a subsequent cell. Depending on the functions of the cells their morphology may vary [1, 2].

Glial cells surround neurons and have various functionalities including acting as the general and structural support for neurons. Schwann cells and oligodendrocytes insulate axons in the PNS and CNS, respectively [3]. Schwann cells form the myelin sheath which essentially acts as insulation around a nerve fiber, referred to as myelination. Fibers may be myelinated or unmyelinated and, consequently, they show different characteristics. In a myelinated fiber, large segments along its length are wrapped by layers of myelin while only small segments between the wrapped segments are left exposed at regular intervals. The exposed segments are referred to as the nodes of Ranvier. There are other types of glial cells that are thought to bring nutrients to cells, provide the blood-brain barrier and help maintain the right ion concentration. They also absorb neurotransmitters and some are only recruited during infection, injury and seizure [1].

In PNS, generally, there are two roots originating from the spinal cord. The dorsal root conveys the sensory information while the ventral root conveys the motor signaling. The dorsal root then enters the dorsal root ganglion, a local accumulation of cell bodies and supporting cells. Peripheral axons may be bundled into what is called nerves. The nerves from the dorsal and ventral roots merge to form the spinal nerve. In CNS, cell bodies may be arranged in two ways. Nuclei are the local accumulations of neurons with similar connections and functionalities, such as the collections found in the cerebrum, brainstem, and spinal cord. The second arrangements are cortices which are sheet-like arrays of cells such as those found in the cerebral hemispheres and cerebellum. The axons in the CNS are gathered into tracts, analogous to nerves in the PNS. Tracts that cross the mid-line of the brain and spinal cord are referred to as commissures. The term gray matter identifies any accumulation of cell bodies and neuropils (synaptically dense regions of dendrites, synaptic terminals, and glial cell processes) in the brain and spinal cord (e.g., nuclei or cortices) while white matter is essentially tracts and commissures.

2.3. Afferent and efferent neurons

In terms of functionality or the direction of conveying the neural signal, neurons are classified into three major groups: afferents, efferents and interneurons. Afferents carry information from the periphery of the body to the CNS. These neurons are very often interchangeably referred to as sensory neurons although not all afferent communications may lead to a form

of sensation [1]. Efferents or the motor neurons carry the neural signal and commands from the CNS to muscles and glands. Interneurons, which are neither sensory nor motor, constitute the largest group of neurons [1]. Interneurons convey APs over long or short distances from a neuron to the other.

2.4. Neural circuits, receptors and transmitters

Neurons are organized to form neural circuits and reflexes which may, for instance, process the sensory information and elicit motor responses. A typical circuit on the afferent end may be terminated by sensory receptors. These are nerve endings which transduce specific stimulus energies into the corresponding receptor potentials. Receptors are specialized in terms of the energy they transduce which may be electromagnetic, mechanical, thermal or chemical [4]. A complex sensation such as pain may recruit different receptors. The receptor potential then travels along the attached afferent fiber with a specific AP firing pattern. The attached afferents may covey a specific mode of sensation as well. The cell bodies of these afferents may be in the corresponding ganglia. The central axon of the mentioned cell might enter through the dorsal horn of the gray matter of the spinal cord and synapse with central neurons. Namely, it may synapse with interneurons or motoneurons in the spinal cord.

The basic forms of the synaptic transmission between neurons are electrical and chemical while most of the transmissions are chemical [4]. While at an electrical synapse a low resistance electrical path exists between the two associated cells, at chemical synapses neurons are separated completely by a small space called the synaptic cleft. The entities that essentially pass the neural signal from a presynaptic cell to a postsynaptic cell are called neurotransmitters. The arrival of an AP at the presynaptic side of a synapse leads to the release of chemical neurotransmitters which then diffuse across the cleft and interact with the receptors of the postsynaptic side. This interaction leads to either excitation or inhibition. The former leads to the suppression of the AP generation while the latter leads to the generation of APs. The type of the resulting action, primarily, depends on the type of the transmitter and receptor involved. Also, the synaptic input may add up from various presynaptic cells.

The sensory information may be conveyed through the white matter of the spinal cord to different regions in the brain for further processing. In which case, the response of the brain may be conveyed back to the target cells through different regions of the white matter of the spinal cord. A spinal reflex on its own may result in a motor activity without any modulatory input from the brain [1]. Through the ventral horn of the gray matter, efferent fibers leave and land on target muscles or organs. At a neuromuscular junction, neurotransmitters are released and the corresponding contraction or relaxation effects are mediated.

2.5. Action potential

Having presented an overview of different elements and aspects of the human nervous system, we now discuss the AP as the most fundamental phenomenon in the nervous system further. An AP is a rapid (~1 ms) variation (~100 mV) of the transmembrane potential [1, 3]. APs are naturally triggered in the initial segment of the attachment of an axon to its corresponding

soma and travel down the axon at velocities ranging from about 1-120 m/s depending on the fiber type [4]. Different activities are mediated via this signal throughout the nervous system by the neural circuits mentioned before. The actual command or information is not perceived by the variation of the signal (i.e., AP) but different effects are mediated through the paths APs travel and their firing pattern.

Generally, there are three main temporal phases in an AP. The resting potential, the transmembrane voltage from inside to outside in the absence of any stimuli, is a negative value. Upon an increase in the transmembrane potential beyond a threshold, it rapidly increases to a specific positive value. This phase is called the depolarization period. The AP generation is an all-or-none process, meaning that any rise smaller than the said threshold does not yield such a response. The depolarization phase is followed by the subsequent reduction in the transmembrane potential which is called the repolarization phase. The transmembrane potential reduces even below its initial resting potential for a period which is referred to as the hyperpolarization phase. There exists the absolute refractory period in which no action potential may be triggered in the segment of the membrane under question. This is followed by the relative refractory period during which period a stronger than normal stimulus may produce a new AP [5].

The generation and propagation of APs are mediated by voltage-gated ion channels in the membrane and the subsequent influx and outflow of ions. These channels are ion specific, meaning that when they are open they are only permeable to a specific ion. Also, the state that these channels are at depends on the transmembrane potential. Supposing that two media are separated by an ion specific channel and the density of that ion is different in the two media, ion flows against the concentration gradient. It is noted that ions do not exist in isolation, meaning that a positive ion is paired with a negative one. Thus, as ions that the barrier is permeable to diffuse, assuming a positive ion is diffusing, an electric field is built up in the direction of the concentration gradient. The opposing forces of the concentration-dependent diffusion and electric field reach an equilibrium, at which stage there is no net ion flow. By equating these opposing forces, the transmembrane electric potential at which the equilibrium is reached can be calculated. This is referred to as Nernst voltage. Nernst voltage is measured from intracellular to the extracellular space. Thus, a higher concentration of a positive ion outside the cell results in a positive Nernst voltage for that ion. Where several ion species are present, the transmembrane potential can then be calculated using the Goldman-Hodgkin-Katz formulation. Building on the Nernst equation, if the membrane becomes more permeable to a specific species, the equilibrium potential tends to the Nernst potential of that species. The resting potential is not a case of equilibrium but that of the steady state.

The permeability of channels is governed by the voltage-gated channels mentioned before. The pioneering work of Hodgkin and Huxley (HH) [6] laid the foundation for the existing systematic understanding of the channel mechanisms. By setting the transmembrane voltage to a predetermined value and measure the transmembrane current for the said voltage in the giant axon of loligo, HH formed a set of curves of the conductivity of the membrane to potassium and sodium versus time for various depolarization voltages. Apart from the overall time trace, they noticed that as the clamp voltage increases, the rate at which the conductance

varies increases too. They decided to use first order kinetics (multiple processes if necessary) to fit the experimental data and consider activation and inactivation variables to explain the cessation of conductivity following its initial rise. Although HH developed a merely empirical formulation for the observations but the overall macroscopic system of equations they defined is compatible with the microscopic understanding which exists today [1]. The channels have gates that depending on the voltage across them the rate at which they open or close varies. For a channel to conduct, all its gates should be open. The concentration of the sodium ions in the extracellular space is much more than those in the intracellular space while that of potassium ions is the other way around. Therefore, the opening of the sodium channels results in a rise of the transmembrane potential while the opening of the potassium channels results in its reduction.

Assuming only sodium and potassium ions are involved, a full cycle of the AP generation is described as follows. The inputs in an axon hillock raise the transmembrane potential beyond a threshold at which point the permeability of the membrane to sodium and potassium ions increases. The conductivity of sodium channels increases faster than those of potassium ions. Thus, the influx of sodium ions brings the transmembrane potential closer to the equilibrium potential of sodium ions. At the higher transmembrane potentials, the conductivity of the membrane to potassium ions increases while sodium channels start to inactivate, reducing the membrane permeability to sodium ions. This results in repolarization of the membrane. The inactivation of sodium channels and the prolonged permeability of the membrane to potassium ions result in the lowering of the membrane potential below the resting potential and closer to the equilibrium potential of potassium ions. Several more channel types may be involved in different species but the overall process is generally similar.

When an AP is generated, it automatically induces the generation of other APs in its vicinity [1, 4]. Considering unmyelinated fibers, the extracellular and intracellular current flows along the fiber induce an increase in the transmembrane potential near the depolarized segment. When the AP is induced in a segment of the fiber, the preceding segment is in the hyperpolarization phase, thus, the AP travels in a specific direction. In the case of a myelinated fiber, as the current loops are relatively weak where the myelin insulation is present, the loops are at their highest intensity from a node to the other, resulting in the AP essentially hoping from a node to the other, rendering the transmission much faster. Apart from myelination, fiber diameter also affects the conduction velocity. Larger fiber diameters generally have higher conduction velocities. Depending on the size and conduction velocity of fibers, Erlanger's (Aα, Aβ, Aδ, B and C) and Lloyd's (I, II, III and IV) systems have been proposed for a classification of fibers [1, 4].

3. Fundamentals of neuromodulation

Neuromodulation has two components. The first component involves the delivery of the stimulus current to produce APs in a target neural tissue and the second one is the way this leads to a response. If a nerve is pierced via an electrode and the transmembrane voltage is forced more positive, then APs may be generated. Often, fibers are stimulated by merely perturbing

the extracellular potential. Assuming a cathode–anode pair is placed along a fiber at a distance away from it, the extracellular space near the cathode may become more negative and this forces transmembrane voltage there more positive. This may lead to the generation of a propagating AP in that position. This yields a very simplistic view of electrical stimulation. The actual process is far more complex and requires an understanding of HH type models of the fiber.

In an electrical conductor, charge carriers are primarily electrons while in the tissue they are ions. Thus, electrodes may be thought of as the interface between these two media. It is, therefore, understandable that the processes involved are electrochemical and reduction and oxidation processes may happen at the electrodes which are not infinitely fast and unimpeded. Furthermore, due to the adsorption of charges and redux processes, the interface impedes the flow of current. The contact impedance due to these plays an important role in electrode material selection and design. Enough charge should be pumped into the medium to sufficiently perturb the extracellular potential. When applied as a pulse, the strength and duration of the pulse dictate how much charge is delivered. This leads to the formation of the strength-duration curves that identify a balance between the amplitude and the duration of stimulus pulses. The electrode design, its relative position with respect to the nerve and characteristics of the surrounding tissue, among other features, play a significant role in defining the stimulus pulse design. Moreover, there are safety considerations when charge is injected into the tissue. To understand the dynamics and safety considerations when injection stimulus current through electrodes the following description should be considered.

As an electrode is put into contact with an electrolyte (tissue) a potential develops which is primarily governed by the Nernst formulation and is referred to as the equilibrium potential of the electrode. As the current is injected through the electrode, the potential of the electrode rises above the equilibrium, at which time the potential dependent reversible and irreversible Faradaic processes may occur. Such reactions are dependent on the fastness of the kinetics of the said reactions and the speed of the mass transport [7]. A kinetically fast process with respect to the mass transport requires a small over-potential, defined as the variation of the electrode potential from its equilibrium potential, to lead to a significant amount of current flowing. As the reactants, consequently, do not move away from the surface, applying current in the reversed direction may force the reactions to be reversed (i.e., biphasic charge balanced stimulation). Kinetically slower reactions are limited by the mass transport. Thus, the reactants move away from the surface as the reactions occur at higher over-potentials [7]. These reactions are referred to as the irreversible Faradaic processes while those involving kinetically fast processes are reversible. One of these irreversible processes is the electrolysis of water. This may happen above and below a certain positive and negative potential, respectively, for a given electrode material. The range of the potential below these limits (i.e., safe limits) is referred to as the water window. The electrolysis of water results in pH changes and gas formation which may lead to tissue and electrode damage. It is noted that electrode material forms a very important feature of the design. The safe limits of the charge injection and the general electrical properties of the electrode should be considered. Under most neural stimulation conditions, the Faradaic processes dominate [8], noting the existence of non-Faradaic currents at the electrode interface as well. Thus, it is important to ensure a given material can safely deliver the required charge. Electrodes may be implanted or surface electrodes may be used. The former

is invasive but the delivery of charge is direct while the latter may be non-invasive but the current have a large spread. Unfortunately, it has been shown that risk versus expected benefit has a linear relationship, the higher the risk the more substantial reported benefits, for different methods of stimulation [9]. This may be attributed to efficacy and selectivity. While non-invasive electrodes are simply conductive patches attached to the surface of the body, minimally invasive electrodes may be designed as needles piercing the skin to deliver the stimulus current. General classes of invasive electrodes for PNS in increasing order of invasiveness include extraneural, interfascicular, intrafascicular and those relying on the regeneration of the neural tissue in them. Examples of these electrodes are cuff electrodes, flat interface nerve electrodes (FINESs), longitudinal intrafascicular electrodes (LIFEs), transverse intrafascicular electrodes (TIMEs) and various multi-channel electrodes [10]. For the CNS, the general classification of electrodes is superficial/distal and those for deeper structures.

The second component of neuromodulation is the way the stimulus current leads to a desired response from the associated neural circuits. This may be a simple motor response by stimulating the very same motor fibers or may involve much more complex circuits involving PNS and CNS. Thus, in designing the stimulus signal one should also consider the appropriate features that lead to the desired response. This may include, but is not limited to, stimulus waveform and frequency.

4. Example applications of neuromodulation

A very well-known example of neuromodulators is the cardiac pacemaker. Electrodes are inserted transvenously and placed at the targeted chamber of the heart. The pulse generator is placed in a subcutaneous or submuscular position. Electrical stimulus may be applied in a unipolar or bipolar fashion and the process can be synchronized with hearts pace [11].

One of the applications of neuromodulation is for chronic pain management. Transcutaneous electrical neural stimulation (TENS) owing to its simple delivery method has been investigated for many years. Various waveforms and frequencies have been used. The placement of electrodes may be directly over the painful area, its peripheral neural supply, the dermatome of the associated spinal roots and known trigger points. It is thought that the resulting analgesia is due to the activation of central inhibitory mechanisms. For instance, stimulation of Aβ afferent fibers are thought to lead to inhibition of nociceptive C and Aδ afferent fibers in some cases. Examples of devices developed based on TENS concepts include NEMOS (Cerbomed GmbH, Erlanger, Germany), a portable device that targets the auricular branch of the vagus nerve via electrodes placed on the concha of the outer ear, Cefaly (CEFALY-Technology, Seraing, Belgium), a wearable device for supraorbital stimulation by a bipolar electrode patch on the forehead and gammaCore (electroCore LLC, NJ, USA), a handheld noninvasive vagal nerve stimulator, all for the treatment and management of migraine. Spinal cord stimulation using implanted electrodes [12], occipital nerve stimulation using implantable electrodes [13], transcranial magnetic stimulation [14] and transcranial direct current stimulation [15] have also been used to treat various neuropathic pain patients.

Deep brain stimulation (DBS) is one of the key applications of neuromodulation that has found applications in treating Parkinson's disease [16], essential tremor [17], dystonia [18], Tourette syndrome [19], chronic pain [20], epilepsy [21], Huntington's disease [22] and even mental disorders [23] with different sites of stimulation. A linear electrode array is implanted deep in the brain. In many of the above cases the exact mechanisms that lead to desirable outcomes using DBS are not known due to the complexity of neural circuits in the brain. However, its efficacy has promoted its use and further research.

A very successful example of neuromodulators is the cochlear implant [24] in which the auditory nerve is stimulated via electrodes placed on a flexible platform that is placed in a layer of the cochlea (basilar membrane). Sound is recorded externally and upon processing the stimulation paradigm is inductively transmitted to the electrodes. Sound as a mechanical wave hits the tympanic membrane (i.e., eardrum). Ossicles, three bones connected to the tympanic membrane, convey this motion to the cochlea which is filled by fluid. At a layer of the cochlea there exists the basilar membrane which is stiff and narrow near the ossicles and wide and flexible on the other end. Due to this structure, the thinner segments *resonate* with higher frequencies. The hair cells on the basilar membrane then translate this to a neural signal which is conveyed through the auditory nerve. The basilar membrane may be appropriately stimulated to induce hearing perception.

Visual prosthesis is another example of using neuromodulation to restore function. One of the most common forms of blindness in the developed world is neural blindness. This is generally due to the loss of photoreceptors. In many cases part of the neural circuits between the receptors and the brain survive and this may be harvested to restore vision. Light passes through the cornea, pupil and lens and is shone on the retina. Retina is covered by photoreceptors (rod cells, more populous and specialized for dim light and cone cells, for bright light and colors) that transduce light to a neural signal which goes through the visual pathway to be perceived in the visual cortex of the brain. Electrical stimulation may be delivered in various places [25]. The stimulation may be delivered via epiretinal [26], subretinal [27] or suprachoroidal [28] electrode arrays. Stimulation may be delivered by deriving the appropriate pattern via an external sensor like camera and transmitted via an inductive link to the array or the photo sensors may be integrated with the electrodes. Stimulus current may also be delivered to optic nerve [29], lateral geniculate nucleus [30] or even the visual cortex itself [31].

Electrical stimulation may be applied to restore or rehabilitate motor function. In this case it is referred to as functional electrical stimulation (FES). While not in all cases of FES a neural reflex may be modulated, due to its significance we briefly discuss it here. FES may be delivered via implanted electrodes [32], percutaneously [33] or transcutaneous [34] in various places. FES have been used in a variety of applications such as improving activity after stroke [35], chronic heart failure [36] or control and rehabilitation of extremities following spinal cord injury [37] or other forms of neural disease.

Neuromodulation may be used to treat various lower urinary tract dysfunctions that arise upon spinal cord injury. A more elaborate description of such interventions is presented as a case study in designing a wearable neuromodulator later in this chapter.

5. Common features of wearable neuromodulators

The introduction to key underpinning concepts surrounding neuromodulation and the key applications presented in this chapter reveal the great potential of the method in improving the quality of life for patients in a variety of patient groups. However, the concept of wearable neuromodulators in terms of their defining features should be further discussed.

In most devices currently advertised as wearable neuromodulators such as Senza system (Nevro Corp., CA, USA) for spinal cord stimulation for pain relief, a range of products from Bioness (Bioness Inc., CA, USA) for improved mobility, Stimwave (Stimwave Technologies Inc., FL, USA) for pain relief, Bionode (Bionode LLC, IN, USA) for glaucoma, Reliefband (Reliefband Technologies LLC, PA, USA) for nausea treatment, various products from Bioelectronics (BioElectronics Corporation, MD, USA) for pain management, Quell (NeuroMetrix Inc., MA, USA) for pain relief and Cefaly (CEFALY-Technology, Seraing, Belgium) for migraine, portability, in a sense that they do not impede the normal life of the user, appears to be the primary common factor. The other common feature of these technologies is that they have a controllable interface with the user, even if this is simply for turning the device on or off. While most of the wearable neuromodulators are non-invasive but this is not necessarily a common feature among all the neuromodulators referred to as wearable. For devices whose electrodes are implanted higher efficacies are expected but various challenges including the risk of surgery, possible electrode migration and power delivery to internal unit should be tackled.

6. A case study

This section presents a brief case study on designing a wearable neuromodulator for treating LUT dysfunctions after SCI.

6.1. Functions of the LUT

The main functions of the LUT are to store and periodically void urine. These functions are performed by the main functional units of the LUT. These functional units include the urinary bladder and an outlet consisting of the bladder neck and urethra. The urinary bladder is engulfed in a smooth muscle called the detrusor while the urethra, the projecting tube from the bladder, is composed of smooth and striated muscles. During the storage phase, the urinary bladder relaxes while its outlet contracts and during the voiding phase the bladder contracts while the outlet relaxes. These synergic and reciprocal activities of the functional units are controlled by complex neural circuits [38].

6.2. Neural control of the LUT

Current understanding of neural control of the LUT is based on studies on various species. This section aims to draw a simple picture of the way the circuits are thought to be formed. The associated neural circuits are primarily controlled in the brain, spinal cord, and peripheral

ganglia. The intricacy of the neural circuits is partly due to LUT functions being under the somatic as well as autonomic control and partly due to the required switching action between the reciprocal activities. Four types of neurons are thought to be involved in the neural control of the LUT functions: the primary afferent neurons, spinal efferent neurons, spinal interneurons and neurons in the brain. These neurons activate or modulate the reflexes [38].

The autonomic nervous system controls the LUT through the sympathetic nervous system, primarily via the hypogastric nerve, and parasympathetic nervous system, primarily via the pelvic nerve. The somatic control of the LUT is mediated by the pudendal nerve. It is generally thought that the activation of the sympathetic nervous system is responsible for maintaining continence while the activation of the parasympathetic system facilitates voiding [39]. Various excitatory and inhibitory neurotransmitters and the associated receptors are involved in the healthy function of the LUT.

Intrinsic properties of the detrusor, leading to low and constant intravesical pressure during the storage and filling, inhibition of the parasympathetic outflow to detrusor, activation of sympathetic efferents to the outlet and pudendal efferent activities are some of the features that might contribute to continence based on studies on various species. Spinal and supraspinal reflexes activated by afferent activities are thought to mediate these. Upon voluntary decision for voiding in healthy adults, the sympathetic and somatic outflows are inhibited and the parasympathetic efferents are activated to facilitate voiding by an initial relaxation of the outlet and the subsequent contraction of the reservoir [38, 39].

6.3. LUT after SCI

The spinal cord is the major pathway through which efferent and afferent command and information travel between the brain and the body. The spinal cord contains longitudinally oriented spinal tracts (white matter) surrounding its central areas (gray matter) where most of the spinal nerve cell bodies are located. The gray matter is organized into segments that comprise sensory and motor neurons. As briefly discussed earlier in the chapter, every segment of the spinal cord is generally in charge of controlling a specific part of the body and functionality. Thus, damage to a specific segment of the spinal cord may result in the loss of control in the corresponding part of the body.

SCI may be divided into two major groups. Tetraplegia is the impairment or loss of motor and/or sensory functions in the cervical segments of the spinal cord due to the damage of the nervous system within the spinal canal. Paraplegia is the impairment or loss of motor and/or sensory functions in the thoracic, lumbar or sacral segments of the spinal cord. Neurological level of injury refers to the most caudal segment of the spinal cord with normal sensory and anti-gravity motor function on both sides of the body provided that there is an intact sensory and motor function rostral to that position [40]. SCI may also be divided into incomplete and complete. In an incomplete injury there is a preservation of some sensory and/or motor function below the neurological level that includes the lowest sacral segments. In contract, a complete injury refers to the situation when there is an absence of any sensory and motor function below lesion [40].

Given the intricate neural circuits involved and the switching-like somatic control of the LUT functions, it comes as no surprise that after SCI both functions of the LUT may be significantly disrupted. Depending on the location of the lesion and its completeness the degree of LUT dysfunctions and their nature may vary. After SCI above a lumbo-sacral level, understandably, the input from higher orders in the brain and, consequently, the voluntary control of the LUT may be disrupted. After a period, new sacral spinal reflexes develop. It is thought that these reflexes are mediated by C fibers which are generally thought to be mechanically silent in healthy individuals but become sensitive to low volume bladder activities after injury. Thus, contractions occur during the filling phase of the bladder [41]. Major conditions appearing after SCI include the neurogenic detrusor over activity (NDO) and detrusor sphincter dyssynergia (DSD). The NDO involves the existence of bladder contractions at low volumes and the DSD is the condition in which the reciprocal activities of the bladder and the outlet are not maintained, hence bladder contractions are mirrored with contractions in the urethra [41]. If untreated, these conditions may have severe consequences for the patient.

6.4. Existing solutions

Solutions to the NDO and DSD may be divided as pharmaceutical, mechanical and surgical. Mechanical devices may be subdivided into passive and active devices. The latter are primarily the kind of devices used for the neuro-muscular stimulation. In the case of the NDO, typically, the first devised treatment involves anticholinergic drugs [42]. High doses of prescribed anticholinergic drugs may lead to troublesome side effects including dry mouth, blurred vision, constipation and cognitive impairment [41]. If such drugs do not yield the desired response, more intrusive interventions, including surgical operations, may be devised. Bladder augmentation, an operation in which a section of the intestine is used to increase the bladder volume, can be used to partially suppress the NDO [43]. For the DSD, catheterization, pharmacologic agents, injection of botulinum A toxin, urethral stents, artificial sphincters, sphincterotomy, which is a complex procedure in which urethra is cut into several times to incapacitate it, are some of the key options [42, 43]. Intermittent catheterization, developed in the twentieth century, is the predominant solution used in tandem with drugs for NDO and voiding. The major issue with catheterization is that it is the foremost cause of re-hospitalization due to infection in the people with SCI [42, 43].

The application of electrical stimulus current to treat LUT dysfunctions has been extensively explored at various sites in the body. The stimulus current may target the excitable tissue of the bladder directly in the form of an intravesical stimulation or bladder wall stimulation to facilitate voiding. Such solutions may be used in patients with damaged lower motor neurons in which cases the neural stimulation is not possible [43]. As an example for stimulating other sites, Finetech-Brindley system (Finetech Medical Ltd., Welwyn Garden City, UK) is a solution for sacral anterior root stimulation [44] for voiding. Efferent fibers, supplying both the detrusor and urethra, are stimulated by implanting electrodes intradurally or extradurally, resulting in the contraction of both. However, when the stimulus is removed the urethra relaxes much faster than the detrusor and this leads to voiding. This voiding would be non-physiological but yields high voiding efficiencies. For the solution to be effective, posterior

http://dx.doi.org/10.5772/intechopen.76673

rhizotomy has been performed in subjects to increase the bladder capacity and compliance by suppressing hyperreflexive contractions of the bladder. Unfortunately, this irreversibly eliminates the reflex erection, reflex micturition and any remaining pelvic sensation. To treat hyperreflexive contractions of the bladder, Interstim system (Medtronic, MN, USA) for sacral nerve neuromodulation has been implemented by delivering a low frequency and low amplitude stimulus via an electrode set, usually placed near the S3 spinal nerve. The effect has been attributed to the inhibitory modulatory effect of somatic afferents on motor fibers to the bladder. Other examples are tibial nerve stimulation to suppress the NDO and the pelvic nerve stimulation to facilitate voiding.

Efferent and afferent pathways of pudendal nerve innervate various pelvic structures including the external anal sphincter, external urethral sphincter, genitalia and urethra. The nerve is paired and its lateral branches originate from both sides of the sacrum. Through the lower part of the left and right sciatic foramen, the nerve's lateral branches enter the gluteal region. Turning around the sacrospinous ligament near its attachment to the ischial spine, the pudendal nerve re-enters the perineum via the lesser sciatic foramen. Running across the distal edge of the ischioanal fossa, the nerve gives rise to its terminal branches in an area referred to as the Alcock's canal [45, 46]. The branching pattern and the course of the nerve have been shown to be highly variable across different individuals [47]. Pudendal nerve stimulation for LUT dysfunction in SCI patients at various positions along the course of the nerve, through different terminal branches and using various stimulation parameters has been the topic of research by many workers [48–55]. A key point is that depending on the position and frequency of the stimulus current pulses, voiding or inhibition effects may be achieved. Also, the pattern of the stimulus pulses may induce different responses. These may be attributed to pudendal afferents being involved in both voiding and storage reflexes.

6.5. A wearable device

The course of the pudendal nerve provides the opportunity of its trans-rectal stimulation using an ano-rectally worn probe with surface electrodes. If electrodes are positioned near the ano-rectal junction, it is likely to expose the compound pudendal nerve to the stimulus current. This way, it may be possible to devise a wearable solution to treat various bladder dysfunctions after SCI. Another interesting feature of this solution when used to improve continence is that the efficacy and viability of the solution may be improved using conditional stimulation in SCI [56]. The majority of cases of the NDO after SCI are accompanied by the DSD [41]. Thus, any contraction in the bladder is mirrored by contractions in the external urethral sphincter. It has been shown that electromyogram (EMG) signal recorded from the external anal sphincter may be used as a surrogate for that of the external urethral sphincter which demonstrates the onset of the hyper-reflexive contractions of the bladder [57, 58]. Due to the closeness of these sites the recording and stimulation may be performed by surface electrodes mounted on the same probe.

Intra-anal and vaginal stimulation is primarily used for an acute delivery of the stimulus current to pelvic structures and for therapeutic purposes. An early attempt to stimulate the

pudendal nerve trans-rectally reported current levels were as high as 100 mA to yield a visible response [59] which is in agreement with more recent results [57]. This might impede the chronic use of the solution. Knight et al. [57] based on a patented technology [60] for conditional trans-rectal neuromodulation of the pudendal nerve and inspired by an earlier study by Brindley et al. [61] in a study on 6 SCI patients suffering from the NDO and DSD showed that by the conditional neuromodulation of the pudendal nerve, hyper-reflexive contractions of the bladder were suppressed. The control signal was set to be the EMG signal from external anal sphincter. They designed the probe more suited to chronic use by considering the anatomy of the anal canal and making the probe from silicone rubber with stainless steel surface electrodes. However, still high levels of required stimulus current were reported. **Figure 1** shows the probe used in experiments.

The study presented by Knights et al. [57] similar to previous studies was not tested for prolonged use. For chronic use, high levels of the stimulus current may result in the habituation of the nerve even under the conditional stimulation. For sensate individuals, such levels of the stimulus current may be beyond the pain threshold and at high levels of the stimulus current the targeting accuracy required may be lost. Any structure in the vicinity may also be stimulated, resulting in unforeseen responses. Also, high levels of the stimulus current increase the possibility of electrode or tissue damage. Therefore, the design of electrodes should be optimized to minimize the stimulus current. Even if the current is minimized, however, the challenge is that the course of the nerve is highly variable between different individuals as discussed earlier in this chapter. Furthermore, the pelvic structures move depending on the posture of the individual. This adds to the variations of the course of the nerve with respect to the device. Using computational model we designed [62] an electrode setting that based on modeling results may be capable of activating the pudendal nerve at much lower thresholds considering all the factors described above. Such models implement what is referred to as hybrid models in the literature. The electrical potential field generated by the stimulation electrodes is simulated in a volume conductor model then the field is applied to more realistic HH type cable models of the nerve to predict their response.

The other feature regarding this solution is the recording compartment. Various studies have investigated different features of surface EMG signal recorded from the external anal sphincter [63]. However, the design of the recording electrodes should be carefully carried out to

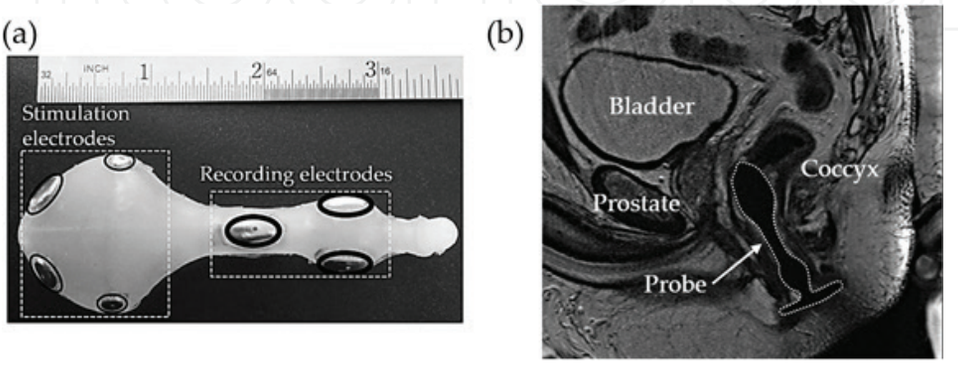

Figure 1. (a) The device used by Knight et al. [57] and (b) the MRI of the device *in situ*.

ensure the recording is selective enough, sufficient EMG amplitudes are recorded and surface electrodes maintain contact for chronic use. In a proof of concept study we demonstrated [64] a design that met the aforementioned criteria.

These led to the design of a new prototype to be tested in the subsequent clinical tests. An issue to bear in mind is the design of the electrode-bearing probe in terms of variability of the anatomy in different individuals. This should be further tested in a population of the patient group. Upon successful clinical trials the electronics may be embedded in the probe to have a fully autonomous wearable solution.

7. Conclusions

Neuromodulation is an interdisciplinary field that draws from expertise in various fields and is currently predominantly used for medical purposes. Neuromodulation may be applied to various cites of central or peripheral nervous system and the applications may range from treatment of mental disorders to incontinence upon SCI. Most existing neuromodulators may be classified as wearable as they are mostly compact, portable, may utilize connectivity and may have a control interface for the patient. However, if one is to exclude invasive devices from this category only a select group utilizing surface electrodes will qualify as wearable. Unfortunately, evidence shows that non-invasive neuromodulators tend to have lower efficacies primarily as the neural tissue is not directly accessed. Future directions may involve devising design strategies that improve the efficacies of non-invasive neuromodulators or reducing the risks associated with invasive ones.

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