Role of Voltage-Gated Sodium Channel Modulators in Peripheral Nervous System Disorders

A project submitted by

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To The Department of Pharmacy

In partial fulfillment of the requirements of the degree of

Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Student ID

Approval

The thesis titled “Role of Voltage-gated Sodium Channel Modulators in Peripheral Nervous System Disorders” submitted by Sabekun Nahar Mithila (17146031) of Spring 2017 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on March 22nd, 2022.

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Ethics statement

Without any doubt, I, Sabekun Nahar Mithila, ensure that the project work entitled "Role of Voltage-Gated Sodium Channel Modulators in Peripheral Nervous System Disorders" is submitted for the fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.) from the Department of Pharmacy, Brac University, under the supervision of Md. Tanvir Kabir, Senior Lecturer, Department of Pharmacy, Brac University, and this study comprises neither human nor animal trials.

Abstract

In current therapy for controlling peripheral nervous system disorders, one of the milestones is the voltage-gated sodium channel modulators. They have higher efficacy with improved side effects. They target the channel and their different subunits to modify the nerve impulse by allowing sodium ions. Selective drugs and biological products are used as modulators to limit the negative effects of disorders. Some drugs may either activate or deactivate the channels by altering the voltage-gated sodium channels pore. Moreover, biological products like alkaloids, marine toxins have a crucial role in understanding binding sites with actions on the sodium channel. Researchers are investigating numerous isoform-selective drugs in treating peripheral nervous system-related disorders. In this report, detailed information about the modulator's ongoing research on the active field is also elucidated.

Keywords: VGSC; peripheral nervous system disorders; voltage-gated sodium channel modulators**;** marine.

Dedication

The paper is sincerely dedicated to my parents, to my sibling, friends and my project supervisor, Md. Tanvir Kabir.

Acknowledgement

With respect and appreciation, I am grateful to the people and would like to thank them for helping me to complete my paperwork. Firstly, I would like to thank the Almighty for giving me the strength, knowledge, and ability to accomplish my thesis paper. Secondly, I am extremely grateful to my supervisor Md. Tanvir Kabir, Senior Lecturer, Department of Pharmacy, Brac University for giving me this opportunity to complete my paper. Without his guidelines, support and patience, I might not finish accordingly. Moreover, I would like to express my deepest gratitude to Prof. Dr. Eva Rahman Kabir, Honorable Chairperson, Department of Pharmacy, Brac University for allowing me to complete my paper. Finally, I would like to thank my family and friends for their love, support and to encourage me to work harder.

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List of Acronyms

PNS	Peipheral Nervous System
VGSC	Voltage gated Sodium Channel
AP	Action Potential
GBS	Gullian-Barré Syndrome
AIDP	Acute Inflammatory Demyelinating Polyradiculoneuropathy
AMAN	Acute Motor Axonal Neuropathy
CIDP	Chronic Inflammatory Demyelinating Polyradiculoneuropathy
SLE	Systemic Lupus Erythematosus
DPN	Dibetic Peripheral Neuropathy

Chapter 01

Background

Our nervous system is liable to identify some changes that occur in both the internal and external environment of the body, to conduct and integrate every single piece of information and accordingly respond to the stimuli. Whereas in the nerve, Schwann cells produce myelin sheath that carries electrical signals along the axon, which initiate action potential and causes polarization of the cell. When myelinated axons get damaged due to some negative effects of the outside environment, medical conditions, traumatic injury, exposures to toxins, pathological factors, then associated disorders might take place. In certainty, voltage-gated ion channels and ion pumps are abundant in axolemma that exhibits electrical excitability along the axons stem (Stassart et al., 2018). These channels are large essential proteins that act as an entrance to allow the ions to control the excitability of neurons.

In most cases, when the sensory, motor, and autonomic nerves form mixed nerves by joining together, they cause various peripheral nervous system disorders. Besides, neurodegeneration is an indication for most neurological disorders and involves peripheral nervous system (PNS) disorders. Moreover, in the peripheral nervous system, the main attribute of various degenerative disorders is an alteration in proteins function, folding mechanism, and metabolism (Bittner et al., 2020). Disorders associated with PNS cause traumatic injuries like pain, inflammation which results in immobility, prickling, weakness in the muscle, etc. Due to the following traumatized injury, a potent inflammatory action arises by activating a series of events in both the central nervous system (CNS) and peripheral nervous system (PNS) (Mietto et al., 2015). However, for degeneration and regeneration this inflammatory action is essential in PNS.

Membrane potential can be modified by some voltage-gated ion channels while neurotransmitters bind at the synapse. Among all the channels of ion, the voltage-gated sodium channel (VGSC or Nav) is capable of transmitting signals by generating action potential (AP) along the axon. As a consequence, they allow Na+ influx, which causes depolarization Additionally, it becomes difficult to reach and open the VGSC threshold if there are no depolarization; as a result, neuronal fire and action potential will not occur (Angus & Ruben, 2019). Nonetheless, cells have a refractory period where Nav is inactivated and unable to produce further AP.

In the field of drug discovery, Voltage-gated sodium channels (VGSC) have created a remarkable change due to their modulators' broad therapeutic spectrum (Tomašić et al., 2013). Hence, VGSC modulators perform a crucial part as they have the ability to either block, activate, or modify sodium ion channels. Moreover, they are responsible to transduce stimuli as well as to initiate and propagate action potential in neurons. Likewise, their modulators can be a drug or biological product, which in turn modify the sodium channel for the influx of sodium ions. There are some marine toxins, venomous animals and poisonous plants that readily exploit this excitatory role by producing toxins that modify Nav channel opening or closing (Gilchrist, Olivera, et al., 2014). They can either block or permit sodium flow to generate or prevent action potential. On the other hand, VGSC modulators may have some selectivity issues, and because of this, they might exhibit consequential side effects. In this case, the precise selection of novel modulators plays a crucial role and is beneficial too. However, it is unclear whether modulating a particular isoform constitutes the primary mode of action (Gilchrist, Dutton, et al., 2014).

When the damage occurs in the peripheral nervous system, peripheral neuropathy may arise. Thus the management pathology of PNS disorders is diverse. The main distinction between the CNS and PNS is; in PNS, nerve fibers can be repaired spontaneously through

regeneration, whereas in CNS, axons do not repair spontaneously. According to the type of damage, recovery patterns may differ in PNS. In this case, voltage-gated sodium channel modulators added an array in the treatment value for PNS disorders and provide an optimization towards a new life for the patients, but it also convey some risk factors, side effects, even some adverse sides.

Chapter 02

Worldwide effects of peripheral nervous system disorders

Globally many people are getting affected by peripheral nervous system disorders. By knowing the epidemiology, affected people elucidating patterns with PNS disorders can be investigated. People with peripheral nervous system disorders suffer from inflammation, trauma, and pain. The majority of the population deal with neuropathic pain ranges from 6.9% to 10%. (Zhu et al., 2020). While considering PNS-SLE which is a sensory or sensory-motor neuropathy, its prevalence value is between 5-27%. Diabetic peripheral neuropathy (DPN) has a significant impact on both mortality and morbidity rate. All classes of people mostly old people are affected by it. Conversely, with age affected person rate are increasing, and mostly males are getting affected by it. Yearly all over the world, around 1 to 4 people in 100,000 are getting affected with Guillain-Barré syndrome (Hughes & Rees, 1997). Moreover, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) prevalence report significantly varies from 1.9 to 7.7 per 100,000 along, whereas, yearly some incidence is also seen which ranges from 0.15-0.48 per 100,000 (Hughes & Rees, 1997). In a report regarding the control and prevention of chronic diseases of the World Health Organization (WHO), about 80% of death cases can be seen in slow developing countries people due to their lifestyle and socioeconomic deprivation (Rzewuska et al., 2017). Whereas people of all ages, ethnic groups, even both males and females are affected by systemic lupus erythematosus (SLE), more than 90% of new SLE patients are women in their reproductive years (D'Cruz et al., 2007).

Chapter 03

Evaluation of neuropathic pain related to peripheral neuropathy

In our body, when the free nerve endings of unmyelinated fibers stimulate significantly, extreme pain or sensory perception emerges. Further, this pain may arise due to any kind of internal injury, chemical or inflammatory effect that sensitizes a peripheral nerve and causes damage to the skeletal muscle. As a consequence, difficulty in motion arises with alteration of posture. According to the researchers and physicians, the term "assessment of neuropathic pain," can be referred to one of two types: 1. assessment of the intensity, as well as the quality of pain with possible treatment-induced changes, 2. analysis of neuropathic pain (Scholz et al., 2009). Moreover, by using some assessment tools, pain can be estimated which include neuropathic pain scale, Leeds assessment of neuropathic symptoms and signs (LANSS), neuropathic pain questionnaire, painDETECT, ID-pain and the Douleur neuropathique (DN4) (Callin & Bennett, 2008). These are called screening tools used for specific clinical assessments. Additionally, for pain assessment, some physical examination can be done that includes evaluation of motor function, pain sensation, and autonomic dysfunction. This physical examination helps to determine the exact area of pain and several sensory deficiencies towards the stimuli.

In many cases, nociceptive pain apprises the event of tissue damage, where neuropathic pain occurs due to the damage that appears in the nervous system. For the suspected patient with peripheral neuropathy, assessment can be done along with conducting blood tests, metabolic rate profile, blood glucose test, thyroid test, vitamin B12 test, imaging tests, nerve function tests, nerve and skin biopsy.

Chapter 04

Disorders affecting peripheral nervous system

The peripheral nervous system involves two vital parts, which include: 1) control involuntary movement called autonomic nervous system, 2) control voluntary movement and regulate the information from a different area of the body to the CNS called somatic nervous system. When dysfunction in axon and myelin sheath is seen in the peripheral area, the transmission of nerve impulses may be delayed or stopped. As a result, signals cannot be carried along the nerve fibers to the peripheral part of the body. In this case, peripheral nerve disorders might appear, such as acquired demyelinating diseases, inherited demyelinating diseases, and axonal. Neurological disability can arise due to demyelination by degeneration of axons and blocking the electrical conduction. In this disorder immune system attack different parts of the body and damages the myelin sheath, which in turn causes the loss of signal transmission for motion and sensation.

In case of PNS nerves, they are mainly made up of the sensory, autonomic, motor nerves. The axon remains unimpaired in demyelinated neuropathies but the fragments of myelin sheath may be impaired. On the other hand, in axonal neuropathies, loss of motor and sensory axons can be seen while myelin sheath remains intact. Apart from this, due to physical injury including trauma, surgery, stress peripheral nerves can also be damaged. Numerous diseases, such as Carpal tunnel syndrome; some autoimmune disorders are responsible for the damage of nerves. Furthermore, some people have PNS disorders by birth. There are some disorders that may affect the PNS in various ways. They can cause damage to more than one nerve.

Names of some disorders are listed below:

1. **Guillain-BarrÉ syndromes (GBSs):** It is a rare infectious immune-mediated disorder. Here demyelination arises in PNS when myelin-forming cells are attacked

by the immune system of the body. As a consequence, signal transmission may be inhibited in the nerve that may affect the muscle function. In Western populations, the clinical picture of GBS is usually produced by acute inflammatory demyelinating polyradiculoneuropathy, but a small percentage of cases are due to acute motor or motor-sensory axonal neuropathy (Hughes & Rees, 1997). It primarily affects the feet, legs and continue to spread to upper side of the body which further results in muscle weakness as well as ascending paralysis.

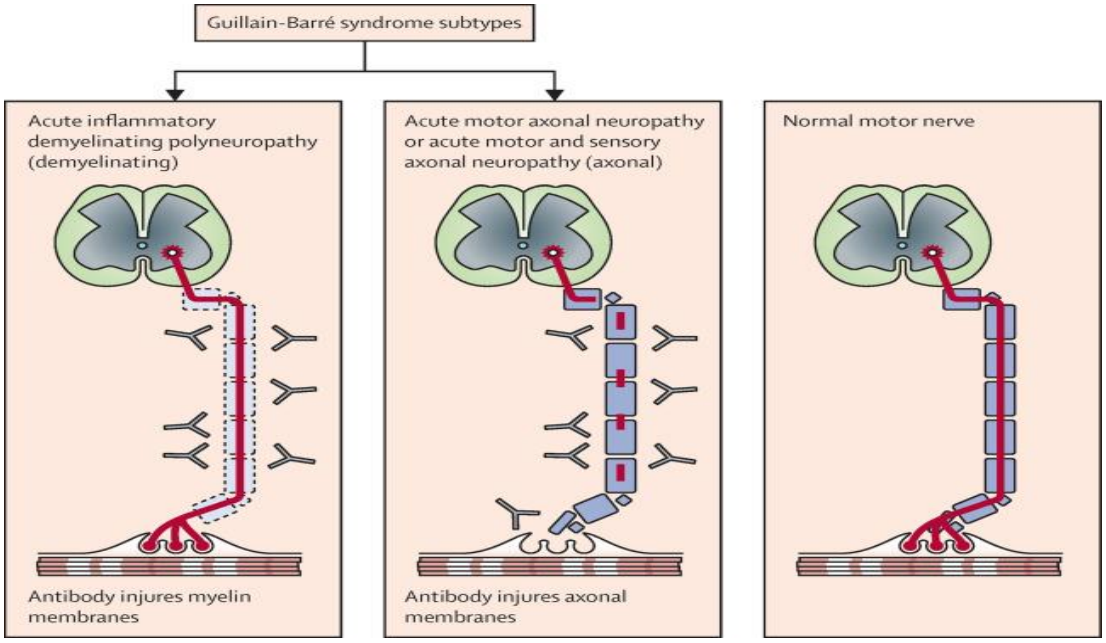

Figure 1- Visual representation of Guillain-BarrÉ syndrome (Willison et al., 2016)

Guillain-BarrÉ syndromes (GBSs) has some unique variants and some of the disorders are discussed below:

I. **Acute motor axonal neuropathy (AMAN):** In AMAN, inflammation does not take place, and dysfunction arises in the axonal part of the neuron; but there will be no demyelination in the axon. Even though block in conduction is the basis of demyelination due to segmental demyelination, but this is not always associated with demyelination. (Lewis, 2007). This block in conduction caused by inactivating the function of sodium channel at the node without even demyelination. AMAN often follows infection with the enteric bacterial pathogen *Campylobacter jejuni* (Hafer-Macko et al., 1996). AMAN is distinguished by the decreased magnitude or lack of distal compound muscle action potentials (CMAPs), indicating axonal degeneration. (Kokubun et al., 2010).

II. **Acute inflammatory demyelinating polyradiculoneuropathy (AIDP):** It is characterized by lymphocytic and macrophagic infiltration with destruction of myelin. Its severity is mainly seen in elderly patients due to the infection such as C. jejuni which causing an inflammation in the affected area. This variant is mostly found in Europe and North America. Because of its early symptoms, it can cause motor dysfunction of body.

2. **Diabetic peripheral neuropathy (DPN):** In today's world, diabetes has become one of the global epidemics. It mainly occur in patients with diabetes, high blood sugar and carbohydrate level found in blood. Autonomic dysfunction is one of the characteristic manifestations of diabetic neuropathy, and can be life-threatening (Said, 2007). This autonomic dysfuntion control internal organs by causing nerve damage. Diabetic autonomic neuropathy causes silent myocardial infarction which shortens patients' lives, about 25–50% of people died within 5-10 years. (Bansal et al., 2006) It

mainly weakens the lower part of the body such as the limb and older patients are mostly effected by it as it causes nerve damage and severe pain. After the nerve injury, the connection is disrupted as a result, it affects the sensory function of neurons.

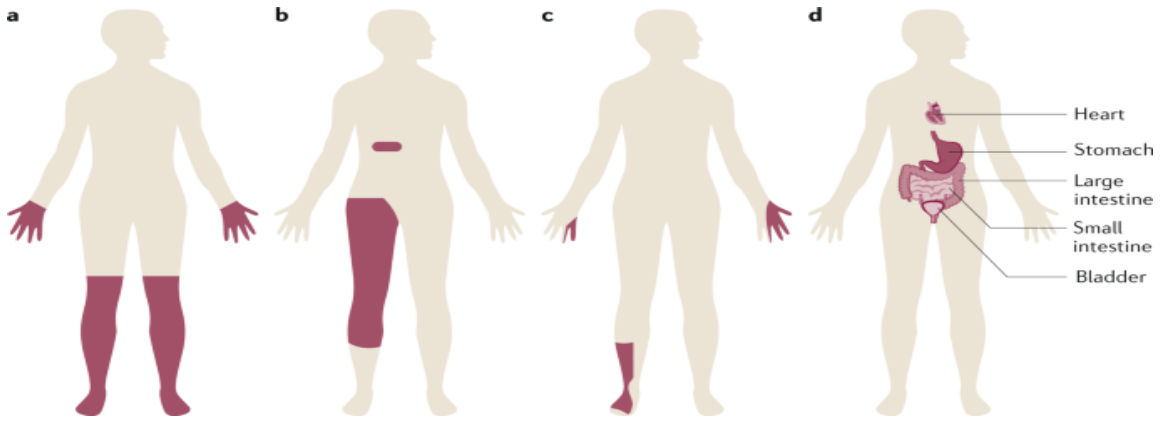

Figure 2- Visual representation of diabetic peripheral neuropathy (Feldman et al., 2019)

3. **Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP):** CIDP is an immune-mediated inflammatory diverse condition that affects the roots of nerve, plexuses, and peripheral nerve trunks (Rajabally et al., 2017). CIDP includes the involvement of motor also sensory. As it is an autoimmune disorder, it attacks its own healthy tissue in case of invading organisms. Moreover, in this disorder, mechanisms such as humoral immune mechanisms with T cell-mediated mechanisms are concerned and attack myelin along the axon. Further, nerves extending via the spinal cord transmit sensory information and contraction back from the joints; skin to the rest of the body. When it is demyelinated, electrical impulses slower down, which become difficult for the nerve to transmit messages from the brain.

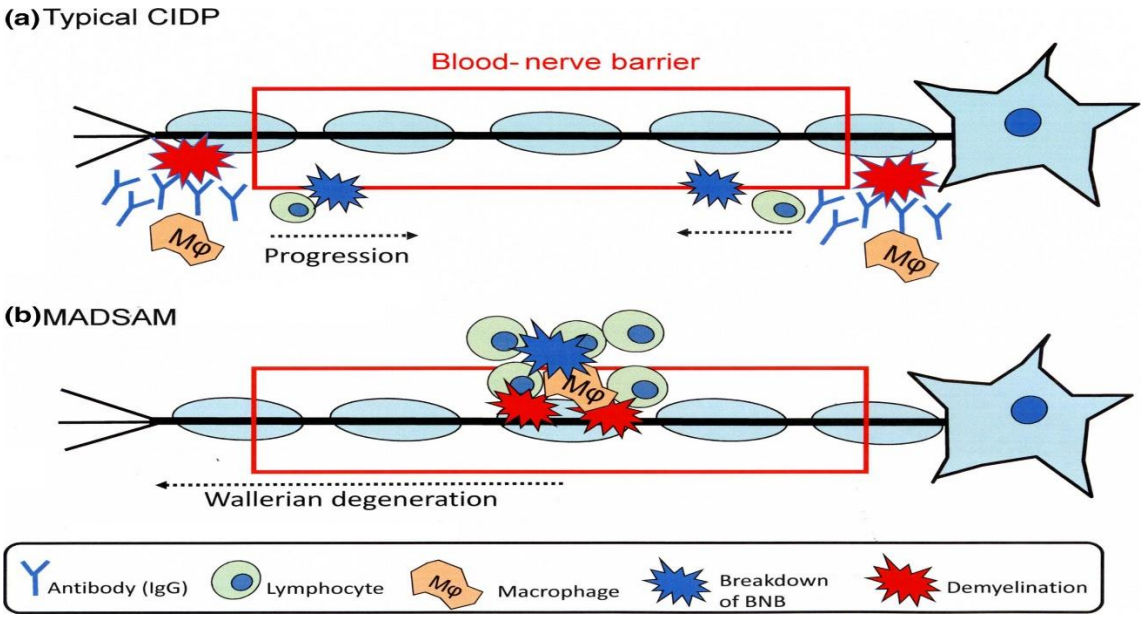

Figure 3- Visual representation of chronic Inflammatory Demyelinating Polyradiculoneuropathy (Kuwabara et al., 2018)

4. **Systemic lupus erythematosus (SLE):** Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease with protean clinical manifestations that may affect any organ or system (Gordon et al., 2010). It causes an affects in PNS via antibodies that block the blood flow to nerves. It further controls the inflammation of the nerves or the tissue around the nerves. About 6.9% of patients' involvement has been noticed with the peripheral nervous system. It highly affects kidney, tendons, joins, blood vessels, and skin. However, depending on the type and damaged area, its prevalence varies.

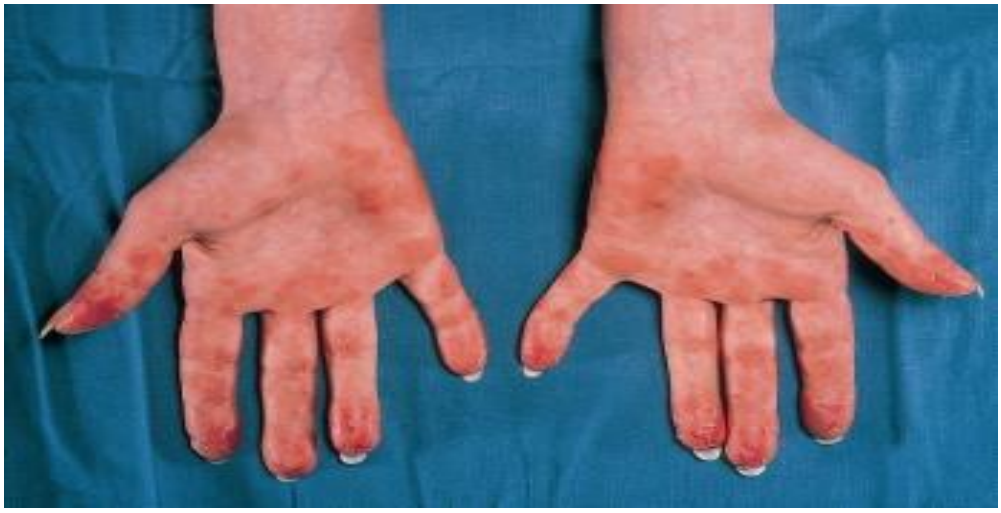

Figure 4- Visual representation of systemic lupus erythematosus (Gordon et al., 2010)

Chapter 05

Pathogenesis and risk factors of disorders affecting peripheral nervous system

Peripheral nervous system disorders can occur for various reasons, but some factors are associated with these disorders where risk factors increase the chance of developing a disease. However, to generate functional peripheral nerves, a combined series of events needs to be achieved for the transmission of signals in sensory and motor nerves. (Previtali, 2021). In maturation, if any unusual event occurs, then as a consequence, it might cause an effect on the functioning of the nerve that develops peripheral neuropathy. Similarly, it can also arise from infection, toxins, drug choice, trauma, and many more.

The following disorders pathogenesis and risk factors are given below:

Diabetic peripheral neuropathy: It is very common in diabetic patients. However, glycation has a linkage with the pathogenesis of DPN. Even every part of peripheral nerve tissues is glycated in this case. Further, these glycation end-products exist in axons, Schwann cells, and endoneurial vessels as deposition. When the density of myelinated axons reduces, the potency of deposition increases. These glycation end-products possess toxicity in peripheral nerve tissue with progressive endoneurial microangiopathy. Nonetheless, Schwann cells undergo an apoptotic process; by releasing inflammatory cytokines-tumor necrosis factor (TNF-α) or cachectin, which are responsible for creating a high amount of glycation end-products. Recent research has revealed that all stages of diabetic peripheral neuropathy are concerned with vascular factors, as well as metabolic interactions (Cameron et al., 2001).

Apart from this, foot ulceration accompanying amputation in the lower limb can occur because of DPN. Further, DPN risk increases with age when the glucose level is not adequate. According to current research, the duration of diabetes, age, glycosylated

hemoglobin A1c (HbA1c), diabetic retinopathy (DR), smoking, and body mass index are all risk factors for diabetic peripheral neuropathy (X. Liu et al., 2019). Other than that, poor glycemic control, hypertension, insulin resistance, dyslipidemia are the major risk factors.

Guillain-BarrÉ syndromes (GBSs): A distinctive infection can be identified in approximately half of GBS patients, and at least one-third of these infections occur by Campylobacter jejuni or C. jejuni (Van Den Berg et al., 2014). There are some pathogens that can also cause GBS, and these include; cytomegalovirus, mycoplasma pneumonia, influenza A, Haemophilus influenza, and so on. After being infected with C.jejuni , the vital step that arises in GBS is the production of antibodies, which further crossreact with typical gangliosides that do not create in uncomplicated C.jejuni gastroenteritis (Kuijf et al., 2010). From this, anti-GM1 (ganglioside-monosialic acid) and anti-GD1a antibodies go for complement activation by binding at the node of an axon, which forms a membrane attack complex (MAC) to disappear voltage-gated sodium channel. This axonal attack slows down nerve conduction. Moreover, in the peripheral nerve, C. jejuni infection triggers both humoral and autoimmune responses, which results in damage of the nerve and several symptoms.

Regardless, Campylobacter jejuni infection can cause diarrhea which is the risk factor of GBS. Furthermore, Guillain-BarrÉ syndromes can be triggered by the influenza virus, surgery, trauma, COVID-19 virus, Hepatitis A, B, C, and E, Hodgkin disease.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): CIDP caues inflammation, and because of this inflammation, it has been attributed to immune mechanisms. Here damage occurs in the myelin layer of the peripheral nerve that results in inflammatory disorders. This damage occurs when an antibody-mediated reaction by T cells along with macrophages is seen in the layer of connective tissue of the myelin sheath. As a consequence, damage can be seen in some part of myelin sheath of peripheral nerves. It is

likely that both B and T-cell mechanisms are involved (Mahdi-Rogers & Rajabally, 2010). However, in the peripheral part of the immune system, an unknown antigen is presented in the T cell that activates the T cells. As a result, clonal expansion occurs; to release inflammatory mediators that can easily cross brain nerves. By breaking down of BNB, some humoral factors may come out that give endoneurium access. Further damage may be caused by macrophage-mediated demyelination, complement deposition, deposition of C5b-9/membrane attack complex (MAC), subsequent lysis of cell, along with CD8+ directed cells lysis (Mathey et al., 2015).

CIDP is not a fatal disease unless and until the patient goes for any treatment. If not treated accordingly, it can be more prominent to have permanent nerve damage and sensory and motor dysfunctions. Also, some risk factors are associated with CIDP-such as antecedent infections, diet, smoking, drinking alcohol, and coffee increase the chance of having CIPD.

Systemic lupus erythematosus (SLE): In the pathogenesis of systemic lupus erythematosus, aberrant innate immune responses have been contributed to tissue injury by releasing the inflammatory cytokines, also activating the autoreactive T and B cells which results in the injury of end-organ by the production of pathogenic autoantibody (Craft, 2011). These immune responses, however, are linked to the production of cytokines such as type 1 interferon-α (IFN-α). These cytokines are responsible for the maturation of dendrite cells. Mainly type I interferons are primarily produced by innate immune plasmacytoid dendritic cells (pDCs) in response to a viral or bacterial infection (Craft, 2011).

It can affect all age-related people, but pregnant women have a higher chance of possessing this disorder. Additionally, women are more affected by this disorder compared to men. A known risk factor for SLE is exposure to respirable silica dust, for example- the crystalline form derived from quartz as well as some systemic autoimmune diseases like scleroderma

and rheumatoid arthritis (Miller et al., 2012). Genetically, it may be triggered by smoking or around a smoker, too much sunlight, chemicals, infectious agent (viral or bacterial), and hormone replacement therapy. Nonetheless, at the onset of systemic lupus erythematosus, to boost the antigen-specific immune response, vaccination is proposed as a potential catalyst. (Angus & Ruben, 2019).

Table 1- Various types of Peripheral nervous system disorders:

Name of diseases	**Etiology**	**Risk factors**	**Pathology**	**Clinical feature**	**Management**
Acquired-demyelinating disease					
Guillain-Barre syndrome	Unknown	Antecedent infections: Campylobacter jejuni or C. jejuni, Mycoplasma pneumoniae or M. pneumoniae, cytomegalovirus, Epstein-Barr virus.	Segmental demyelination Inflammatory (macrophage, lymphocyte) infiltrates	Acute ascending symmetric paralysis, paresthesia, choking, difficulty in breathing, autonomic dysfunctions (hours to several days)	Supportive therapy, plasma exchange, IVIG
Chronic inflammatory demyelinating polyradiculoneuropathy	Unknown	Autoimmunity	Segmental demyelination Thin myelin sheath Onion bulb	Slow, progressive neurological deficits such as tingling, numbness, symmetrical	Glucocorticoids Plasmapheresis IVIG

			(short internodes) formation Perivascular inflammatory infiltrates	weakness of limbs, paresthesia of limbs, loss of reflex, ataxia, limb incoordination. (slow, progressive)	
Anti-Myelin Associated Glycoprotein (MAG) neuropathy	Due to Immunoglobulin M monoclonal gammopathy		Segmental demyelination, Immunoglobulin deposits	Benign, minimal distal muscle weakness, progressive sensory ataxia, tremors.	Supportive therapy (exercise, balance training) Corticosteroids, IVIG, Plasmapheresis.
POEMS syndrome	Unknown (paraneoplastic syndrome)	Plasma cell neoplasm	Endothelial cell hypertrophy with disrupted	Polyneuropathy (paresthesia, motor weakness, sensory	High dose chemotherapy Stem cell

			tight junction No inflammatory infiltrates No immunoglobulin deposition	disturbance), organomegaly (hepatomegaly, lymphadenopathy), endocrinopathy (testicular atrophy, gynecomastia), paraproteinemia (M-protein), skin changes.	transplant Corticosteroids Alkylator therapy Radiation therapy Supportive therapy
Inherited demyelination disease					
Charcot Marie Tooth disease	Mutations of genes (PMP22, P0, connexin 32, mitofusin-2, etc.)		Segmental demyelination Onion bulb formation	Distal muscle weakness, foot drop, scoliosis, hammer toes, neuropathic pain, fatigue, sensory disturbance	Supportive therapy (exercise, muscle training, balancing)

				(slow, not progressive)	

(Kamil et al., 2019)

Chapter 06

Treatment option to treat peripheral nervous system disorders

These treatment options mainly focused on the relief from symptoms. To treat different types of peripheral nervous system disorders, some signs with symptoms need to be considered. Sometimes, if the dose of any drug is not accurate, then adverse effects may arise, which make the patient's health worse.

The following disorders treatment options are given below:

Guillain-BarrÉ syndromes (GBSs): Early symptoms of this disorder can be numbness, weakness in muscle, pain, and hyporeflexia and balance; on the other side, as days pass, later symptoms can occur such as difficulty in walking, speaking, blurred vision, paralysis, severe pain. This pain can be severe within four weeks. However, immunoglobulins are naturally produced antibodies that help to fight off infections and numerous diseases. When these immunoglobulins cannot produce, then intravenous immunoglobulins (IVIGs) can be administered. Moreover, immunoglobulins must be given as 0.4g/kg equivalent to body weight at least for 5 days. However, according to some controlled trials, IVIG exhibit high potential to enhance muscle strength, to block conduction, and in many neurological disabilities (Jolles et al., 2005). On the other hand, immunomodulatory therapy- such as plasmapheresis; is also applicable in treating GBS. In this plasmapheresis, harmful antibodies are removed that are attacking the nerves. But some studies suggested that patients who received IVIG treatment had more improvement than those with plasmapheresis (IJsselmuiden & Faden, 1992).

Diabetic peripheral neuropathy (DPN): DPN has various symptoms from numbness to neuropathic pain, burning sensation, and weakness in arms or legs. In the management of

painful DPN, the current and initial approach is to maintain the blood glucose level (IJsselmuiden & Faden, 1992).

For long-term prevention from DPN, control in glucose level needs to be strictly followed (Wu et al., 2017). Currently in the US for the treatment of DPN, three types of drug products have been approved, and these are- selective serotonin and norepinephrine reuptake inhibitor (duloxetine), an anticonvulsant (pregabalin), an opioid receptor agonist and norepinephrine reuptake inhibitor (tapentadol-dual effect) (Freeman, 2013). Moreover, an anesthetic drug (lidocaine), analgesic drug (acetaminophen), and non-steroidal anti-inflammatory drug (ibuprofen) can be prescribed. Additionally, to lower blood pressure, regenerate nerves, and in reducing insulin resistance, anti-seizure drugs (topiramate) create an additional value. This anti-seizure drug must give at a lower dose of about 15mg. These medications for DPN can help to relieve symptoms and may prevent complications.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP): It has many signs and symptoms such as headache, nausea, rash, or influenza-like symptoms, meningeal irritation, inflammation, tingling in arms and legs, loss of reflexes and balance. Consequently, various forms of immunotherapy have been tried in its treatment (Mahdi-Rogers et al., 2017). For first-line treatment in combating CIDP, two common primary treatments are corticosteroids as tablets or intravenous infusions; and immunoglobulin. Somehow due to its inflammatory action and slow immune response, corticosteroids (prednisolone) are used to reduce inflammation and to treat various types of conditions like arthritis. In case of headache and skin rash, an infusion; can be given. On the other hand, immunoglobulin can be administered to stop the immune system from disrupting the myelin sheath. Further, plasma exchange therapy can be beneficial to slow down the immune system, and it is a third first-line treatment. When these first-line treatments are inadequate, then azathioprine, cyclophosphamide, cyclosporine, and methotrexate can be given.

Systemic lupus erythematosus (SLE): According to the patient's health manifestation, drugs should be selected. In this disorder, several signs and symptoms can be seen-such as fever, rash, fatigue, joint pain with swelling, anemia, and blood-clotting problems. As a consequence, treatment can be done with NSAIDs; for swelling and pain-immunosuppressants (methotrexate, azathioprine), antimalarial drugs (hydroxychloroquine), and corticosteroids (methylprednisolone, prednisone in low dose) can be given. As a first-line treatment option to survive from SLE, hydroxychloroquine (HCQ) with systemic glucocorticoid (GC) can be administered concurrently for long-term outcomes (Padilla-Córdova et al., 2020). Somehow while taking this HCQ, it may cause toxicity in the retina, so to reduce this side effect, this may be given-5mg per kg daily basis. Further, to reduce inflammation, GCs such as methylprednisolone and prednisone can be given. To avoid adverse events like glucocorticoid-induced osteoporosis, patients can take prednisone doses about <7.5mg per day (Gergianaki & Bertsias, 2018). Management of SLE stands a little bit complex due to its complications and varying options of treatment.

Chapter 07

Voltage-Gated Sodium Channel

An integral protein called VGSC has distributed in the excitable cell. They are found in the axon's initial part and between the gaps of the myelin sheath in high density. In neuronal cells for the generation of excitability and to perform regular physiological processes, VGSC plays a critical role (Wang et al., 2017). It is the key determinant in case of excitability as well as integration of potential within terminals and is responsible for initiating the all-or-none sodium (Na) ion-dependent action potential. To activate VGSC cell needs to depolarize, where at resting state the sodium channel remain close (Eijkelkamp et al., 2012). When it gets activated, an upward movement of action potential arises; in excitable cells. As a result, the quick inward flow of Na ion takes place and, after that, depolarization rise to equal the sodium ion concentration inside the cell by closing the channel. Sometimes, VGSCs are not completely inactivated, which results in a small persistent of Na+ current. The process of activation and inactivations are voltage-dependent. In a sodium channel, a transition from one state to another can happen by knowing the rate and time it takes to remain the channel open or close; this further affects the ion conductance and shape of AP (Savio-Galimberti et al., 2012). These action potentials generate signals along the axons based on myelination and demyelination.

Moreover, by altering either carboxyl-terminus or interacting with β-subunits, channels can be quickly inactivated. But disruption might occur in fast inactivation by interacting α-subunit of VGSC with cytoplasmic protein (fibroblast growth factor). Whereas in low inactivation, some conformational changes can be seen by rearranging the pore of the channel. However, in this case, domain IV with segment 4; and domain II with segments 5 and 6 are related. It is important in the regulation of excitability but quite complex.

There are various isoforms in VGSC that are responsible for different disorders of the PNS, but mostly, VGSC isoforms blocked by TTX, which is referred to as ‘‘TTX-sensitive channels”. These channels are responsible for the activation and inactivation of sodium currents. Currently, in the peripheral nervous system, nine types of VGSC α subunits have been detected except Nav1.4, whereas their level of expression varies according to the type of VGSC α subunits (Savio-Galimberti et al., 2012). There are some subtypes that have the potential to detect peripheral nervous system disorder. Sometimes, one gene contributes to more than one isoform of VGSCs. When mutations arise in the genes, then a wide variety of diseases arise. It has been known from a recently reviewed medicinal chemistry perspective that, several drug effects have been studied that target voltage-gated sodium channels as well as used in the assay technology (García-Pérez, 2016).

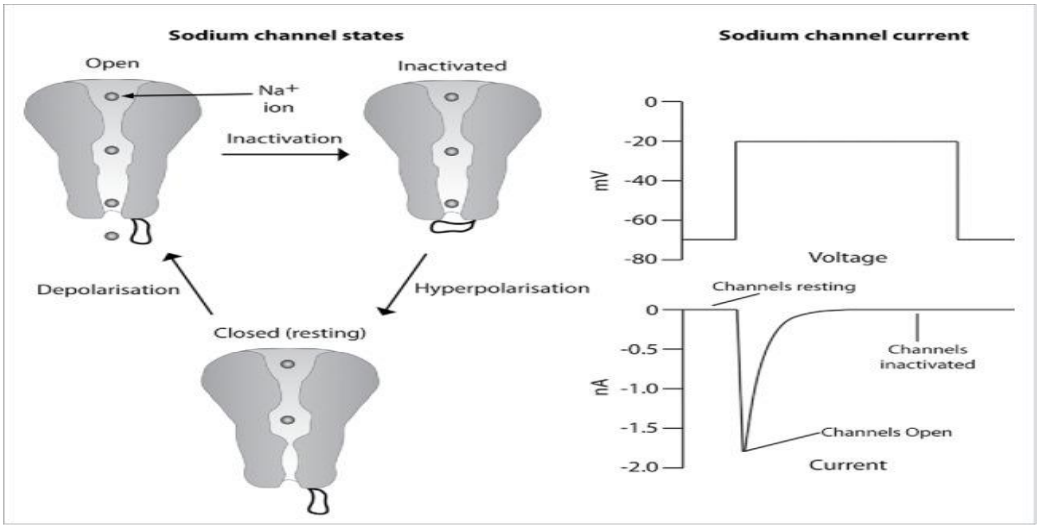

Figure 5- Visual representation of voltage-gated sodium channels (Bagal et al., 2015)

Chapter 08

Structure of voltage-gated sodium channel

When there is some changes arise, a protein network called VGSC is activated. It allows the sodium ion through the channel to generate AP. If there are any delays found in the case of conducting AP, then deficiency might be found within peripheral nerves. VGSC is comprises of alpha and beta subunit.

8.1 α Ssubunit of Voltage-gated sodium channel:

VGSC alpha subunit has three parts which include four highly homologous transmembrane domains, three intracellular loops, and two terminus called N-terminus, C-terminus (NT and CT) (Abriel & Kass, 2005). Moreover, each domain contains six hydrophobic segments and primary one in VGSC. Among these six segments, extremely-sensitive arginine residues (positively charged) reside in segment S4, which do not change with the change of AP; hence it is called a voltage sensor and activate VGSC. Further, some short fragments SS1 and SS2 re-enter the membrane, which is found in between the S5 and S6 segments. In this α subunit, three loops can be seen, where loop L3 contains three hydrophobic residues of amino acid, that include isoleucine, phenylalanine, and methionine. However, the region is involved in rapid inactivation and is also called IFM. VGSC has varying sensitivity towards tetrodotoxin (TTX) which is a sodium channel blocker; as a result, it has two forms.

Till now, from (Nav1.1-NAv1.9) nine subtypes of α subunits have been detected in the PNS, and nine different genes (SCN1A-SCN11A) can encode these subtypes. These subtypes play a significant role in various disorders. Lastly, they are dispersed extensively on peripheral nervous system neurons and related to certain disorders.

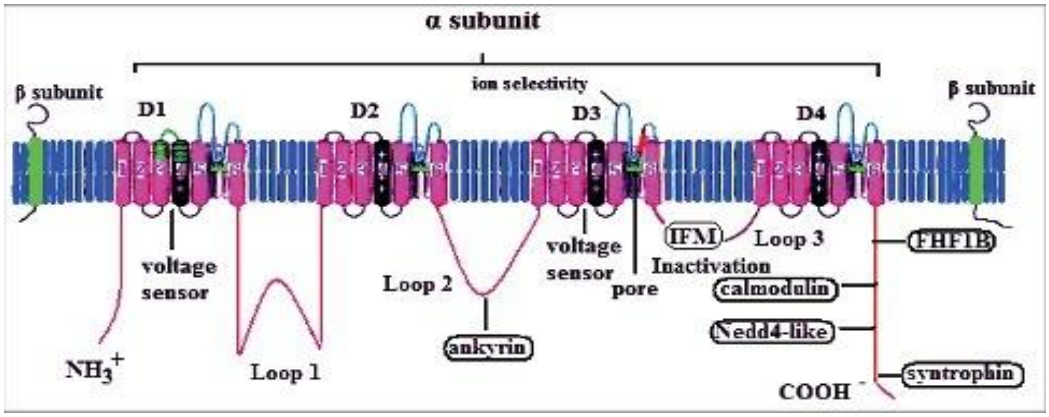

Figure 6- Structure of VGSC α subunit (Abriel & Kass, 2005)

8.2 β subunit of Voltage-gated sodium channel:

This β subunit has three parts and these include; a domain, intracellular small terminus called C-terminus, and extracellular large terminus termed as N-terminus. Within the nervous systems excitable and non-excitable cells, the β subunit can be found in. They are termed auxiliary subunits as they can regulate α subunit. Additionally, it regulates sodium ions across the cell membrane and has a role in molecule adhesion. For nerve excitability and brain development, the β subunit of VGSC has an adhesive function which includes the processing of neurite outgrowth, determining axonal path, and fasciculation, as well as they, play a similar function in the heart and peripheral nerve (O'Malley & Isom, 2015). Even at the node of Ranvier, with α subunit it is closely bound to modulate the rapid conduction of electrical signals.

In VGSC β subunit is the auxiliary subunit with five subtypes: β1, β1B, β2, β3, and β4, which are encoded by different genes, SCN1B-SCN4B (Mao et al., 2019). Furthermore, with α subunit among four subunits, two subunits bonded non-covalently such as β1 and β3, whereas the other two subunits bonded covalently such as β2 and β4. While on the contrary, β1B is a soluble molecule of the β subunit. In the structural formation of VGSC, β subunit has no

contribution, but they do take part in the alteration of the voltage-dependent sodium channel and its kinetics.

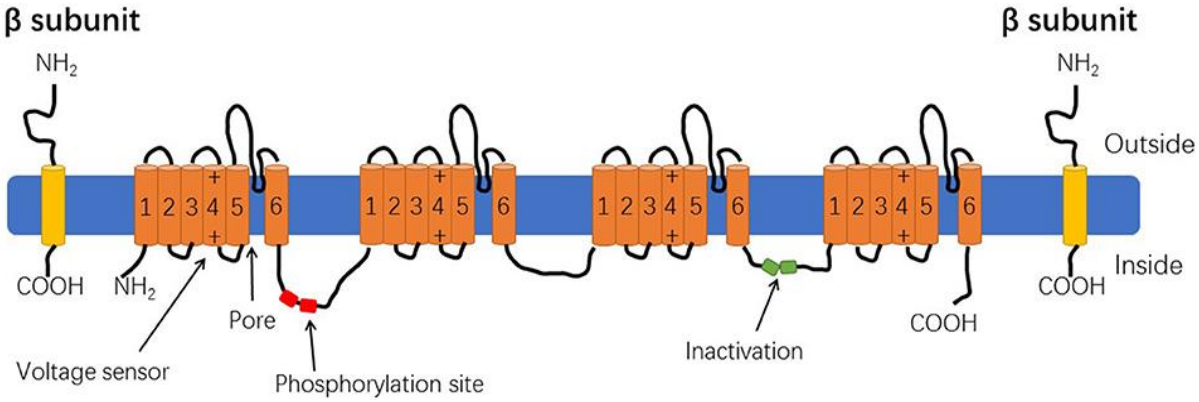

Figure 7- Structure of VGSC β subunit (Mao et al., 2019)

Chapter 09

Sensitization in voltage-gated sodium channel

In chronic pain, VGSC have a significant function, but an alteration in their expression may lead to changes in their sensory neurons along with some accumulation at the injury site. Moreover, after the injury of the nerve, some posttranslational modifications occur in VGSC, which finally lead to peripheral sensitization.

After a tissue injury, an immediate response is required, and this response is the indication of peripheral sensitization, and it works by reducing the threshold of the neurons. In peripheral sensory neurons, TTX-sensitive enhances the manifestation of Nav1.3. Nerve injury is associated with hypersensitivity, and by reducing the expression of Nav1.3, this sensitivity cannot be lower. In VGSC, two subgroups can be found according to the TTX sensitivity, and these include tetrodotoxin-sensitive groups and tetrodotoxin-resistant groups, whereas TTX-resistants are Nav1.5, Nav1.8, and Nav1.9, and rests are TTX-sensitives (Zhang et al., 2018). In a peripheral sensory neuron, the subtypes of VGSC such as Nav1.8 along with Nav1.9 are found. Nav1.8 TTX-resistant protects sensory neurons from depolarization by blocking AP. On the other hand, Nav1.9 is consequential in generating spontaneous firing near the resting potential. TTX sensitive sodium channels are insensitive towards the toxins when treated with a drug.

Nonetheless, peripheral sensitization mainly increases the sensitivity of mechanical stimuli of nociceptors as a consequence of functional alteration in the properties of nociceptors. Furthermore, they can also be sensitized by nerve growth factor (NGF), which, in turn, causes more AP. Hence, by blocking nerve growth factor (NGF) and receptor of tyrosine kinase, peripheral mechanical sensitivity can be inhibited.

Chapter 10

Voltage-gated sodium channel modulators

The modulators of voltage-gated sodium channels (VGSC) contains broad therapeutic potential as a result, VGSC targeted during drug discovery (Yoshida, 1994). Under some pathophysiological conditions, some inflammatory mediators are involved in the modulation of VGSCs function and expression. These modulators either block, activate, or modify sodium ion channels. In VGSC, some neurotoxins have six sites of action, where one side is for the receptor. In this receptor site, some local anesthetics; antiarrhythmic drugs (class I) are bound. Besides, blocking agents of VGSC can easily block the channel by pore alteration, which disrupts the flow of sodium ions and the channel possess little or no effect in the case of resting state.

10.1 Drugs as modulator

Mechanism of action of lidocaine:

Neuropathic pain, resulting from injury to the peripheral or central nervous system, is due to up regulation of aberrant sodium channels with neuronal hyper-excitability (Moulin et al., 2019). In this case, local anesthetic agents such as lidocaine can play a significant role as it is a sodium channel blocking agent. Lidocaine suppresses ectopic discharges in injured DRG or peripheral nerves (Hermanns et al., 2019). Ectopic firing is responsible for neuropathic pain and can be decreased when a systemic dose of lidocaine is given; to inhibit the propagation of nerve impulses.

The principal mechanism of action of lidocaine as a local anesthetic is through blockade of voltage-gated sodium channels (VGSCs) leading to a reversible block of action potential propagation (Hermanns et al., 2019). To easily permeate through the membrane, they are found in the un-ionized form. In the case of ionized form, it blocks VGSC by binding with its

prime alpha subunit. Whenever lidocaine binds with VGSC, they interrupt sodium influx through the channel; as a result, AP generation and propagation are inhibited. From this, polarization is also reduced, and without depolarization, no initiation or conduction of pain signal can occur, and patients can temporarily relieve from chronic peripheral neuropathic pain. They rapidly bind with VGSC; hence, the onset of action is faster.

Mechansim of action of lacosamide (LCM):

Lacosamide was approved in 2008 as an anticonvulsant and for the treatment of diabetic neuropathic pain (Knapp et al., 2012). It is an anti convulsant. However, lacosamide (LCM) is a recently developed sodium channel blocker (SCB), which acts mainly on the slow activation state in sodium channels (Kim et al., 2019). This slowdown of inactivation occurs when the depolarization is prolonged. Lacosamide shifts the slow inactivation voltage curve to more hyperpolarized potentials and accelerates the entry of the sodium channels into the slow inactivated state (Porter et al., 2012). Due to such slow inactivation, fewer effects are found than other drugs with fast inactivation. Because of this, lacosamide has fewer side effects compared to other drugs.

Uses of lidocaine and lacosamide in peripheral nervous system disorder

Several drugs are there for neuropathic pain, which is associated with numerous disorders like DPN. Lidocaine lowers the production of specific inflammatory cytokines to exert an anti-inflammatory response. Further, lidocaine patch is effective is effective in DPN to relieve chronic pain on the feet. Further, topical lidocaine, a sodium channel blocker, has been recommended as a first-line treatment for localized peripheral neuropathic pain, used alone or in combination with another first-line treatment (Wolff et al., 2010). Additionally, lidocaine can be given in a variant of GBS. Lidocaine-medicated plaster appears to be effective for controlling paresthesia and painful burning sensations in patients with

erythromelalgia-like presentations of AASN (Gales et al., 2016). On the other hand, lacosamide can be given in pain. Also, it was discovered as an antiepileptic drug and capable of reducing DPN (M. S. Chong & Hester, 2007).

10.2 Marine toxins as modulator

Mechanism of action of tetrodotoxin (TTX):

Conotoxins largely found in tropical marine cone snails and are small peptides. These peptides have a diverse range of pharmacological targets, including membrane ion channels like VGSCs (Knapp et al., 2012). Among all conotoxins, only four conotoxins target VGSC. However, some of it block VGSC, as a result, sodium ions cannot pass through the channel. On the other hand, δ- and ί-conotoxins are responsible for the activation of the channel and trigger neuronal firing by interacting with the hydrophobic surface residue and domain IV of VGSCs.

There are thousands of naturally found toxins that can modulate the sodium channel. However, some neurotoxins can block VGSC, and these are TTX, saxitoxin, ciguatoxins, whereas some toxins may activate the VGSC to allow the flow of sodium inside the cell, such as batrachotoxin and natural pyrethroid. In marine and terrestrial animals, especially puffer fish, voltage-gated sodium channels (VGSCs) are blocked by a potent non-peptide guanidinium neurotoxin called tetrodotoxin (TTX) (González-Cano et al., 2021).

TTX inhibits sodium flow in nerves and muscles as they are potent inhibitors. Their binding affinity with the VGSC alpha subunit inhibits Na+ ions flow. They act by blocking the initiation of AP; as a result, paralysis may arise in nerves and muscles. TTX-sensitives can block VGSCs subtypes Nav1.1-Nav1.7, whereas TTX-resistant can block three subtypes of VGSC. In the VGSC pore, binding affinity altered the exchange in dielectric. The VGSC P-loop, some negative charges (glutamic acid, aspartic acid) reduce the sensitivity in TTX and

cause a substitution in the ring. Substantial reduction in TTX-sensitivity was produced by isoforms of TTX-sensitive channel, while at the same site, TTX-resistance channel isoforms secured TTX-sensitivity by reducing aromatic ring residue (H. L. Chong & Ruben, 2008). This substitution hindered the indirect binding affinity of TTX.

Uses of tetrodotoxin (TTX) in peripheral nervous system disorder

For hypersensitivity in peripheral pain, TTX can be a potential analgesic intervention related to TTX-sensitive NaV isoforms (Chong & Ruben, 2008). It is well tolerated and safe up to 45 micrograms but higher than that may cause systemic toxicity. It has high potency in reducing hyperalgesia and allodynia. Also, against neuropathic pain, especially cancer-related pain, TTX is most effective while ensuring safety (Hagen et al., 2011).

10.3 Alkaloids as modulator

Mechansim of action of alkaloids:

Veratridine is an alkaloid neurotoxin found in sabadilla plant seeds that modulates sodium channels to elevate the influx of sodium ions. As a result, a huge amount of sodium ions enters the VGSC, which modifies the channels to remain open at resting potential. In addition, some side effects-tingling, and numbness; influenza or colds with congestion; pulsating headache with related PNS disorders can be minimized by taking veratridine. Furthermore, the modulating effect of veratridine on sodium channel properties reported for skeletal muscle Nav1.4 as well as murine vas deferens myocyte Nav1.6. But it is very unfortunate that for NAV1.7 its effect is slightly known (Q. Liu et al., 2018). Also, they are responsible for the blockage of sodium channels with the changes in threshold activation so that they can be open at resting potential.

On the other hand, an indole alkaloid called koumine isolated from Gelsemium elegans shown various pharmacological actions, for example, antitumor, anti-inflammatory, anxiolytic, and analgesic activity (Jin et al., 2014).

Moreover, Moreover, marine alkaloid clathrodin is considered to be a modulator of voltage-gated sodium (Nav) channels (Peigneur et al., 2014). It has therapeutic potential on the selectivity of VGSC isoforms. They can either block or activate the inward flow of sodium by targeting some isoforms in the excitatory nerve.

Uses of alkaloid in peripheral nervous system disorder

Alkaloids have a significant part in human medicines and health. If considering veratridine, it is a steroidal alkaloid to treat peripheral pain. They have also anesthetic and anti-inflammatory effect. Where koumine has a high therapeutic index with low toxicity. It can be used in DPN causing pain by inhibiting the flow of sodium and ectopic discharge from VGSC. Moreover, they can alter the pathway involved in hyperglycemia. However, these alkaloids have a huge role in DPN by reforming the functions of nerves and by reducing inflammatory actions in neurons.

Chapter 11

Peripheral nerve voltage-gated sodium channelopathies

In the human genome, VGSC structure-related subunits contain some isoforms that are encoded by genes. Like α-subunit, isoforms are encoded by ten genes, and these start from SCN1A-SCN11A; whereas β-subunits are encoded by four genes, and these start from SCN1B-SCN4B. VGSC structure can be affected if any mutation occurs in any of these genes. These mutations can further develop channelopathies. In the peripheral nerve, mutations of these channelopathies mainly occur due to the following genes with specific isoforms; Nav1.7-Nav1.9 in genes SCN9A-SCN11A. Aforesaid these isoforms are related to neuropathic pain and inflammation. Due to an increase in nerve excitability, neuropathic pain occurs, which might cause changes in VGSC properties. Nerve injury with pain can alter the trafficking of the sodium channel gene expression. Such changes can cause the cell to be hyper-excitable during pain.

Pain in nervous system can cause injury or disorders to the somatosensory nervous system. In the peripheral nervous system, subtypes of VGSC from Nav1.7-Nav1.9 have been found and appear to play a key function in neuropathic pain development (Porter et al., 2012). Particularly, this peripheral neuropathy are associated with some mediators and that is Nav1.7. The Nav1.8 sodium channel has recently been discovered to be a component of the molecular machinery involved in the mechano-transduction of joint pain and associated pain disorders (Schuelert & McDougall, 2012).

Nonetheless, erythromelalgia causes an effect on the PNS that results in pain and occurs due to a mutation of gene SCN9A. When any kind of shifting takes place toward more negative potential, it activates the voltage-dependent. Further, due to this activation, hyperexcitability

may arise. Whereas due to some mutations, channels can be inactivated, resulting in a high amount of current and a slow down of depolarization.

Chapter 12

Schematical Representation of Project Methodology

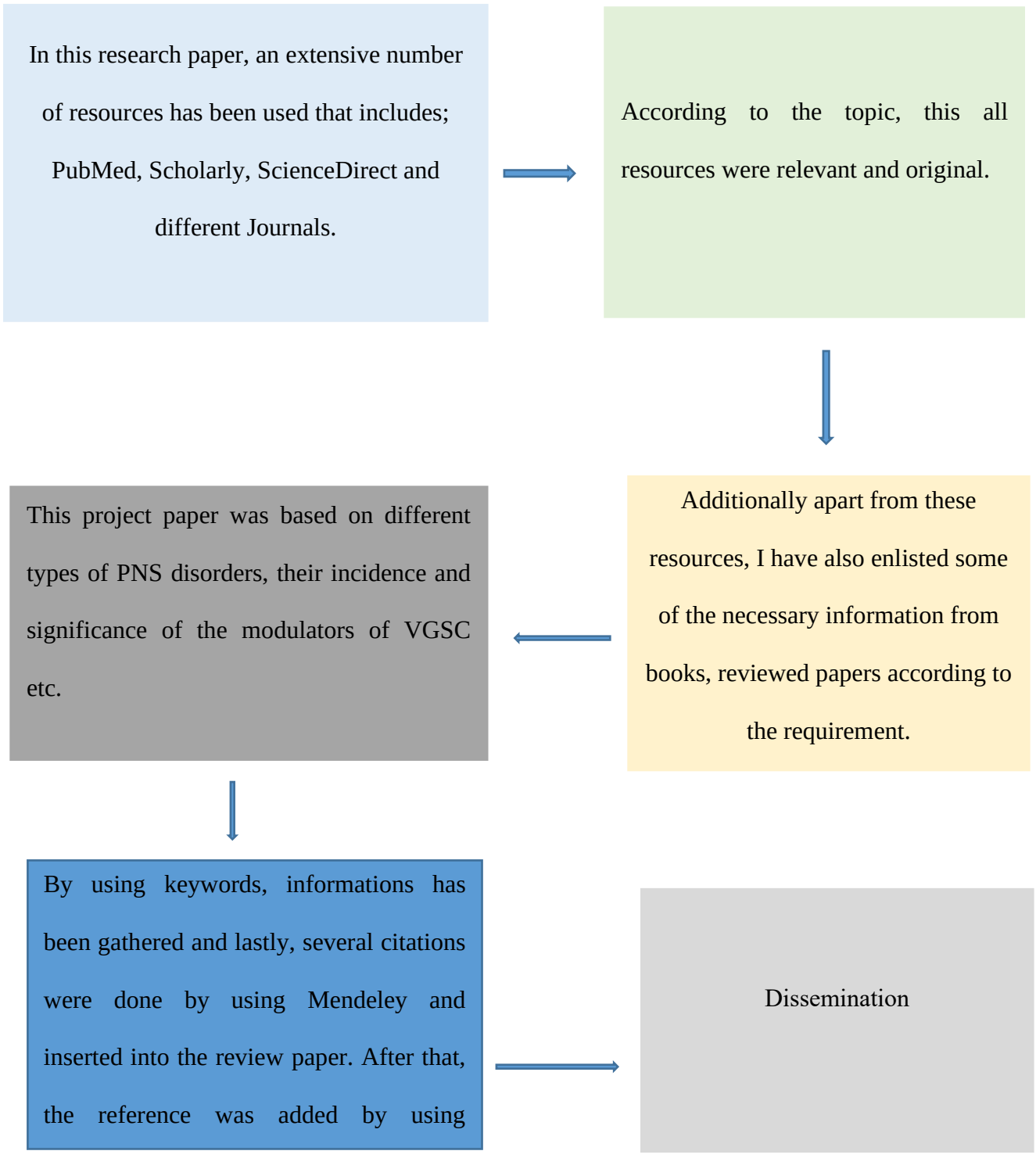

Figure 8- Schematical Representation of Project Methodology

Chapter 13

Future work

Voltage-gated sodium channel modulators has given a new array towards research. There are many alkaloids, toxins and venoms which can be useful modulators in near future. Moreover, discovery of isoform-selective modulators are now a major focus of attention in the analgesic field. But it is challanging to discover a compound which show isoform selectivity with minimal dose limiting side effects. It has created a broad area to scrutinize for understanding between sodium channel isoforms and potential selective modulators. Further, isoform-selective sodium channel modulators have a lot of patent activity which need to interpret through some clinical assessment. Moreover, voltage-gated sodium channel antagonists exhibit significant activity in the upcoming research field. However, by understanding the 3D crystal structure of VGSC will create a new outlook in the of discovery. Recently, some novel, selective toxins on VGSC subtypes has been synthesized which exhibit drug like characteristics.

Chapter 14

Conclusion

Nerve signaling exhibit a significant role in PNS, if any complications arise during the conduction of electrical signals, then it might create some negative impact on the body. An action potential generates these signals along the axons. Due to axonal dysfunction, many peripheral nervous system disorders may arise with associated side effects. But, disease-related factors and related treatments are helpful in the management of disorders. However, modulators of VGSC create a new field in treating patients with PNS disorders. They modulate the action potential of channels, so that flow of impulse can easily be propagated. Numerous new drugs along with biological products are available as sodium channel blockers and activators which have the potential to alter sodium channels. In the end, the aim of this paper is to point out the modulators as an option for the treatment of patient suffering from PNS disorder and relationship with VGSC.

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