**Biochemistry of Nervous system: An Overview**

Authors: Sanghapriya Pal1, Kiran Dahiya2

1. Senior Resident, Department of Biochemistry, Maulana Azad Medical College, New Delhi. India
2. Professor, Department of Biochemistry, Pt. BD Sharma PGIMS, Rohtak, India

**Abstract:** The nervous system is one of the most complex system in human body with presence 100 billion neurons, several million axons and dendrites. The system mainly consists of two types of cell- neuron and glial cells. Several researches have made us to understand the function of neuron and their synapses, particularly their electrical impulse generation and propagation, while breaking the myth of glial cells being only supportive in function. Moreover, the presence of stem cells in CNS challenges the old concept of nervous system being a non-mitotic tissue. Various molecular cell biology techniques have enabled us to better understand the functioning of the system as well as molecular aspects of various neurological pathology. The knowledge of stem cell and molecular neurobiology are being continuously exploited for the purpose of diagnosis and treatment of different neurological diseases.

**Introduction:**

The nervous system of human is approximately 2.4% of adult body weight and 83% of it is brain. This system helps us to communicate with the environment, to perceive the response and to act accordingly. The brain is the command center- which regulates all the voluntary and involuntary function. It is the organ of consciousness, cognition, ethics and behavior. Among the genes encoded in human genome, more than one third are expressed in nervous system. Moreover, the system composed of over 100 billion neurons, several million miles of axons and dendrites and more than 105 synapses. There are also variety of glial cells which have important role in synthesizing myelin, maintenance of homeostasis, immune-regulation in addition to supportive role. The brain uses about 103 to 120 grams of glucose per day. In spite of these complexities, modern biochemistry, molecular biology and various other aspects of molecular neuroscience have been trying to understand this system with outstanding researches. In this chapter, biochemical basis of functioning of nervous system and their implication in various neurological diseases will discussed.

**Nervous System:**

Nervous system is divided into two:

1. Central nervous system (CNS): consists of brain and spinal cord
2. Peripheral nervous system (PNS): consists of peripheral nerves, those are - i) 12 pairs of cranial nerves and ii) 31 pairs of spinal nerves. This system has two component- a) somatic- cerebrospinal system, b) splanchnic – also called autonomic nervous system (ANS), which is in turn divided into sympathetic and parasympathetic system.

Information flows either of two direction- from periphery to CNS or CNS to periphery. The former is called afferent and the latter one efferent. In afferent, information comes from all the sensory organs (eye, ear, nose, taste buds) and also from joints, muscles, viscera and skin. On the other hand efferent information goes from CNS to various glands, smooth muscles and skeletal muscles.

**Cellular Architecture:**

The cells and their architectural peculiarity underlies the structural and functional complexity of the nervous system. There are predominantly two types of cell population:

1. Neurons:

These are the excitable cells of nervous system. More than 100 billion neurons are found in the brain. They form millions of contact with other neurons. Information i.e. signals are propagated in form of electrical impulse or action potential. From one neuron to other, impulse is transmitted through synapses, the structural and functional connection between two neurons usually formed by axon terminal of one cell, dendrite of the other and glial cell process. The space in between the components are called synaptic cleft.

Organization of neuron: Various types of neuron with different functional significance have the similar structural components. A neuron has a cell body or soma. They are also called perikaryon in which different necessary proteins, neurotransmitters, hormones are produced. It has a nucleus. There is a halo of endoplasmic reticulum (ER) surrounding the nucleus. ER gets stains with Nissl stain, so, is called Nissl substance. A network of microtubule is associated with trans port of materials. Transport from soma through axon is called anterograde transport. Transport from synaptic terminal to soma is called retrograde transport- which is important for shuttling trophic factors mainly neurotrophins. Some viruses like herpes, take advantage of this transport and after getting taken up from nerve ending, they are transported back to soma where they remain dormant. However, input to soma is received by dendrites. There are small spines- the protrusion on which axon makes synaptic contact. Postsynaptic densities on spines contain neurotransmitter receptors. Every neuron has axon originating from axon hillock or initial segment where the AP is formed for next neurons. It is covered with myelin sheath.

Types of neuron: They can be classified on the basis of morphology, size and neurotransmitter they use. Most common is based on morphology:

1. Multipolar neurons: Most abundant type consisting of single axon and multiple dendrites branching from soma. They are found both in brain and spinal cord.
2. Pseudo-unipolar neurons: Mainly found in spinal ganglia. They have dendritic axon receiving sensory information which sent to spinal cord through axon. They help to relat the information from periphery to spinal cord without modification.
3. Bipolar neurons: Mostly found in retina and olfactory epithelium. They consists of one dendrite and one axon. They integrate multiple input and the pass the modified information to next level. They differ with pseud-unipolar on basis of amount of processing of impule in neuron.

Myelin Sheath: Myelin is the multilayered insulating substance around the axons, which allows the action potential to jump between the nodes of Ranvier, along the myelinated segment. It is a lipid rich material formed by the spiraling process of the myelinating cell surrounding the axon, creating multiple bilayers that are tightly apposed by charged protein interaction. A single oligodendrocyte myelinate many axons in CNS, while schwann cell myelinate only one axon at a time in PNS. Different neurological disorders are attributed to the abnormality in myelination. For example, multiple sclerosis is caused by targeting of myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG) by T and B cell respectively. It is important that oligodendrocyte precursor cells do not myelinate axons. Understanding their transcriptional regulation and functional role might be an approach to remyelination and brain repair.

1. Glia:

It was previously thought that glia were only of supportive importance. Later it has been found that glia outnumbered the neurons. In humans, glia to neuron ration is 10:1. Different types of glial cell have been discovered:

1. Astroglia: They are also called astrocytes. They are subdivided into fibrous and protoplasmic astrocytes (found in white and gray matter respectively) and Muller cells (found in retina). The principal function is to support and nurture the neurons. Besides, they are now considered as the contributor of synapses. So, the term tripartite synapse has been introduced. Astrocyte recycle excessive transmitter and regulate signal transmission. Moreover, they can also have neurotransmitter receptors and can also communicate with each other through calcium propagation mediated by gap junction. During development, radial glia a type of astrocytes, is involved in direction and scaffolding for axon migration and targeting.
2. Oligodendroglia: Also called oligodendrocytes. These are the myelinating cells of CNS. One oligodendrocyte can myelinate many axons by wrapping their processes around them. Myelin sheath provides trophic support, protection and proper organization of ion channels with gap at regular interval to allow this, these gaps are called nodes of Ranvier.
3. Schwann cells: They myelinate neurons in PNS. On one hand, like oligodendrocytes they can myelinate but only a single axon at a time, on the other, like astroglia, at neuromuscular junction they take up excessive neurotransmitter and regulate efficient transmission.
4. Microglia: They are derived from monocyte-macrophage lineage and migrate into CNS. They are involved in inflammatory reaction in CNS, can release cytokines on activation. In area of neuronal damage they phagocytose the debris and can act as antigen presenting cells.
5. Polydendrocytes: They are called as glial precursor cells. They are basically stem cells which can generate both the neurons and glial cells. Their activation and recruitment are the first step of remyelination, and so they are in center of research in demyelinating diseases. They also receive direct synaptic input from neuron indicating significant crosstalk between them although it significance is not understood yet.
6. Ependymal cells: These are the epithelial cells lining the ventricles separating the cerebro spinal fluid (CSF) from nervous tissue. They contain cilia on apical surface. Some of them are specialized to produce CSF, are called choroid plexus.

**Blood-brain Barrier:**

CNS remains in a preserved environment where homeostasis has to be maintained for its proper functioning. So, it is necessary to keep CNS protected from rest of the body. This is done by blood-brain barrier. It is formed by endothelial cells linked by gap junctions, their basement membrane, covering of astrocyte processes. This barrier effectively separate the nervous system and vascular compartment. Only small lipophilic molecules, water, gases are allowed to cross. Its clinical significance is that the drugs which can cross this barrier, can be used to treat the CNS diseases.

De Vivo disease is an autosomal dominant disease due to defective GLUT1 transporter of blood brain barrier, resulting in lack of glucose in brain. The associated manifestations are called GLUT1 syndrome. This leads to infantile seizures, delayed development, microcephaly and other mental disorders. Infantile seizures may appear at 1-4 months of age. A ketogenic diet help to control it.

**Trans-membrane potential and propagation impulse:**

The resting transmembrane potential of neuron is -70mV. The question is how this is maintained? One of the contributing factors regarding this are- variability of permeability of different ions such as membrane is very much permeable to potassium (K+) ions, slightly permeable to sodium (Na+) ions and not at all permeable to intracellular anions. The other factor is Na+-K+ ATPase, which transports Na+ out of the cell in exchange of K+. Within the cell the concentration of K+ in more while Na+ concentration is more in extracullular compartment. So, there is a tendency of the K+ ions to leave the cell down their concentration gradient, which is counteracted by inward pull by intracellular anions on K+. This is reinforced by slight permeability to Na+. Thus resting membrane potential is maintained at -70mV. The generation of action potential needs the membrane potential to reach +20 to +30 mV. The event initiated by electrical stimulation causing opening of sodium channel to allow influx of sodium. This is followed by opening of potassium channel. Eventually the resting membrane potential is restored by Na+-K+ exchanging ATPase. The electrical impulse is propagated along the membrane by localized depolarization mediated by localized opening of sodium channel. It is done by conformational change in response to voltage. This causes formation of localized action potential which in turn induce conformational change in neighboring voltage gated ion channels. The previous site has finite recovery time. It is the time taken by ion channels to change their conformation to get closed and reset and by Na+-K+ exchanging ATPase to restore the membrane potential. In this way, the propagation becomes unidirectional.

Along myelinated axon, due to presence of nodes of Ranvier, action potential jumps from node to node. It is because of passive current shuttling in long segment while opening of sodium channels at nodes. This is called saltatory conduction.

Voltage gate ion channels has structural diversity but similarity in the pore forming region, where selectivity filter uses the chemical structure of pore to mimic the hydration sphere of the ions.

Channelopathies: Disorders of ion channels due to some mutation or generation of antibodies against them. This type of pathology might be associated with ataxia, migraine, epilepsy etc. Manifestations are variable but intermittent or paroxysmal feature is very common.

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**Synapse and synaptic transmission:**

A synapse is the contact or communication between two neurons. The information is passed through this synapses from one neuron to the other in terms of action potential or electrical impulse. The synapse can be of different types:

1. Classification based on structural component:
2. Axodendritic synapse: It is formed in between axon and dendrite. It is most common in CNS. The dendritic tree of a multipolar neuron receives many synaptic input which helps the neuron to reach its threshold, generating electrical impulse. This convergence of signals in times and spaces is important and is called temporospatial summation.
3. Axosomatic synapses: Here axon communicate with the soma or cell body. It is less common in CNS. It provides more powerful stimuli as it is more closer to axon hillock, the area of generation of new action potential.
4. Axoaxonic synapses: Axon communicate with another axon. The synapses are often on or near the axon hillock causing very powerful effects.
5. Classification based on mode of function:
6. Electrical synapse: Two neurons electrically communicate through gap junctions. Gap junction is composed of a protein core complex (connexon) through which ions and small molecule can pass. They are mainly found where the group of neurons have to be synchronized as in breathing center or in hormone secreting region of hypothalamus.

Mutation in connexon 32 expressed by schwann cells associated with X linked Charcot Marie Tooth disease. Gap junctions are widely found in glia creating syncytium that protects neurons by removing glutamate and potassium from extracellular environment. Glial calcium waves mediated through gap junctions are associated with migraine aura & march of epileptic discharges.

1. Chemical synapses: It is composed of presynaptic terminal, a synaptic cleft, a post synaptic terminal. When electrical impulse reaches the presynaptic terminal, it opens the voltage gated calcium channel (VGCC) causing the calcium influx. The latter induces the fusion of synaptic vesicles with the presynaptic membrane and neurotransmitters are released by exocytosis into the synaptic cleft. This event is quantal i.e. an impulse causes the exocytosis of fixed number of vesicles. The released neurotransmitter traverses the cleft and binds to the postsynaptic receptors opening a specific type of ion channels. Depending on the type of ion channels the excitatory postsynaptic potential (EPSP) or inhibitory postsynaptic potential (IPSP). An opening of Na+ channel moves the membrane potential toward threshold and opening of Cl- channel moves away from the threshold causing EPSP or IPSP respectively. But a single synaptically evoked potential is not sufficient to fir AP, which is an all or none phenomena. The synapses receiving impulses must close enough and timing must be the same, so that membrane potential can reach the threshold to fire an AP. The post synaptic receptors are of two types:
2. Ionotropic receptors: They are coupled with ion channel. Binding of neurotransmitter causes a conformational change allowing the flow of ions. They are usually multiple subunit structures and fast acting.
3. Metabotropic receptors: They are coupled with intracellular signaling cascade. They acts through G-protein coupled ion channels or second messengers (activating various enzymes like protein kinases). They are usually single subunit structure and function over longer period.

Synaptic Vesicle: Non-peptide neurotransmitters are synthesized anywhere in the neuron, in axon or in cell body. But peptide neurotransmitters are synthesized in cell body only. Neurotransmitters are stored are small or large vesicles in presynaptic terminal. Predominantly small vesicles are present and there are two pools: free and attached to cytoskeletal protein, actin. Small vesicle contains usually contains non-peptide while large one contains both peptide and non-peptide neurotransmitter. The different proteins present on the synaptic vesicle and their roles are as follows:

1. Synapsin: Important to maintain the availability of free small vesicles. They are 9% of total proteins of synaptic vesicles. The synapsin proteins are encoded by two genes. All can be phosphorylated near N terminal end by cAMP-dependent protein kinase and/or calcium-calmodulin (CaM) kinase I. On the contrary to synapsin IIa & IIb, synapsin Ia & Ib can also be phosphorylated near C terminal by CaM kinase II. On arrival of impulse, Ca++ enters through presynaptic membrane and binds to calmodulin and activate CaM kinase I & II ( producing Ca++-CaM kinase I & II) and thereby phosphorylate synapsin and made the free from cytoskeletal protein or prevent the binding of free vesicles. Moreover, calcium-calmodulin directly bind synapsin and prevent its binding with actin and other cytoskeletal protein. In this way, this protein maintains the number of free synaptic vesicles.
2. Synaptophysin: An integral membrane protein of synaptic vesicles involved in formation of channel through which neurotransmitter pass into synaptic cleft.
3. Synaptotagmin: Another integral membrane protein of synaptic vesicles helps in docking of vesicle onto the presynaptic membrane in a calcium dependent process.
4. Syntaxin: An integral protein of presynaptic membrane binds with synaptotagmin and thereby involved in exocytosis along with involvement of Ca++ channels.
5. Synaptobrevin: Also called vesicle associated membrane protein (VAMP). A family of two protein od 18 & 17 kDa, those are present on the cytoplasmic side of the membrane involved in vesicle transport. Tetanus toxin and botulinum toxin binds and cleaves VAMPs causing irreversible inhibition of neurotransmitter release.
6. Rab3: member of rab family of GTP- binding protein. Rab3 is involved in docking and fusion of vesicle with presynaptic membrane. It is held by polyprenyl side chain near C terminal.
7. SV2: Large glycoprotein with 12 transmembrane domains. Function is not clear.
8. CSPs (Cysteine string proteins): Family of chaperones, involved in latter stages of Ca++ mediated exocytosis.
9. Vacuolar proton pump: Involved in transporting back the neurotransmitters into synaptic vesicles after their reformation and release from presynaptic membrane.

**Neurotransmitter:**

Neurotransmitters are the molecules which mediate the transmission of electrical impulse through synapses from one neuron to another. They are carrier of electrical messages. They act either through ionotropic or metabotropic receptors, resulting in EPSP or IPSP formation. They can be usually of two types:

1. Non-peptide neurotransmitter: They are usually amino acids or their derivatives. They are as follows:
2. Glutamate: It is a major excitatory transmitter in CNS. It can interact with NMDA (N-methyl D-aspartate), AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) and kainite receptors. They are named after agonists. All are ionotropic recptor causing an influx of positive charge ion into presynaptic terminal. Excesss Ca++ causes exitotoxicity causing cell death. It is synthesized in neurons from glutamine, excess glutamate is taken up by astrocytes, converting them to glutamine. Later, this glutamine is supplied to neuron for glutamate synthesis. There are some metabotropic glutamate receptors (mGluRs), which can initiate intracellular signaling and increase excitability of postsynaotic terminal.
3. GABA: Gammaaminobutyric acid is the major inhibitory transmitter in brain, present mainly in widespread cortical interneurons and long projection pathway. It is usually synthesized and degrade by GABA shunt. The excess GABA is taken up by astrocytes and converted to glutamine which, in turn, is taken up by the presynaptic neuron. The latter forms glutamate from glutamine.

GABA can bind their receptor (α2β2γ2). GABAA & GABAC receptor both are ionotropic, causing a Cl- influx and thereby an inhibitory response. They can also bind to metabotropic receptor GABAB which activate K+ & inhibit Ca++ channel leading to hyperpolarization.

It is found that in epilepsy its activity is decreased. Valproic acid cross blood-brain barrier and increase the level of GABA in brain. On the other hand, benzodiazepines and barbiturates can bind GABA receptors but on different site.

1. Glycine: This amino acid is the major inhibitory transmitter in spinal cord. It act through ionotropic receptors resulting in Cl- influx, and thereby causing inhibitory response.
2. Acetylcholine: It is present in both PNS (pre- and post- ganglionic parasympathetic and preganglionic sympathetic) or CNS (forebrain); also in neuromuscular junction. They act through two types of receptors: 1) Nicotinic receptors: Ionotropic coupled with nonselective cation channel, 2) Muscarinic receptors: Metabotropic coupled with G-protein signaling pathway.

They are synthesized from choline and acetyl co-A in cytosol of neuron, by choline acetyl transferase. After its action at synapse, it is hydrolyzed by acetylcholinesterase into choline and acetate. The acetate is taken up and metabolized by the tissues.

Lambert-Eaton Myasthenic syndrome: Autoimmune disease having antibody against voltage gated calcium channels (VGCC). There are at least 4 subtypes of VGCC- T, L, N & P. P subtype is involved in this neurotransmitter release in mammals. Research for effective therapy is underway.

Myasthenis Gravis: Characterised by development of autoantibody which interact with the acetylcholine receptors reducing the number of functional receptors and manifested as muscle weakness. Environmental antigen may trigger the event. Thymus might have a role. Although, all these relations with the disease is not clear. Patients are treated by reversible acetylcholine-esterase inhibitor (pyridostigmine), which increase the availability of transmitter at synapse. Steroids, immunosuppressant drugs, anti-idiotype antibody or small nonantigenic peptide (which block the binding of antibodies to receptors) can also be used.

1. Biological Amines: They are group of compounds having amine group in their structure, They are:

Catecholamines: It include domanine, norepinephrine and epinephrine. Dopamine is associated with emotion, motivation, reward etc. It acts through G-protein coupled receptor, D1 (excitatory) & D2 (inhibitory). The other two act through their metabotropic α & β adrenergic receptors. Their action gets terminated by their reuptake and by their metabolism by catechol-o-methyl transferase & monoamine oxidase. The metabolic end product of dopamine is homovanillic acid and of epinephrine and norepinephrine is 3-methoxy-4hydroxymandelic acid. Cocaine inhibit the reuptake of dopamine.

Histamine: Binds to excitatory metabotropic neurotransmitter; involved in wakefulness.

Serotonin: Also called 5-hydroxytryptamine. This is associated with mood, emotion etc. It can be excitatory or inhibitory. Most receptors are metabotropic receptors except one, which is excitatory ionotropic. Its action get terminated by reuptake or by metabolism. First, it is oxidatively deaminated by monoamine oxidases and then oxidized by aldehyde dehydrogenase to 5-hydroxyindole-3-acetate.

Selective serotonin reuptake inhibitors like sertraline, fluoxetine are used to treat depression, they elevate mood by increasing serotonin levels in brain.

1. ATP: It is the energy currecncy of cell. It can also be released by presynaptic terminal along with other transmitters, so it is called co-transmitter. ATP and their degradation product in synaptic cleft, adenosine act by activating P2X & P2Y and there modulate other’s action. That’s why, they are called neuromodulators.
2. Neuropeptides: These are the peptides involved in neurotransmission. They are synthesized as large protein formed in cell body only. Proteolysis of these large proteins form neuropeptides. They are transported to presynaptic terminal by a process mediated by kinesins and myosins. There are two types of axonal transport- fast transport (400mm/day) and slow transport (1-5mm/day). They are involved sensory and emotional responses like hunger, thurst, sex, pain etc. Examples are enkephalins, endorphins, substance P etc. Substance P (one type of neurokinins) is involved in pain perception while endorphins and enkephalins are involved in elimination of pain. Met-enkephalins are derived from N terminal region of β-endorphins. Other neuropeptides invovld in neural response to stress is corticotropin-releasing hormone and adrenocorticotropin.

**Neurotropic factor:**

Neurotrophic factors are the secreted protein those are involved in neuronal growth, differentiation, repair and survival. They can be different types:

1. Neurotrophin family (NT): They act through TrK & p75 receptors promoting the survival of neurons. The family includes nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), NT-3, NT4/5, NT6 etc. It is because of this property, they are, al least theoretically, considered to be effective in disease in which premature neuron death is the pathology like amyotrophic lateral sclerosis (ALS) and other neurodegenerative diseases. Although in growth factors were in effective in human ALS.
2. Cytokine family: It includes cilliary neurotrophic factor (CTNF), leukemia inhibitory factor, interleukin-6, cardiotrophin-1 etc. Knockout mice lacking receptors for CTNF shows experimental motor neuron loss which can be recovered by various groth factors including CTNF, BDNF etc.
3. Transforming growth factor β family: Glial derived neurotrophic family (GDNF), neurturin, persephin belong to it. GDNF is important for the very survival of domaminergic neurons.
4. Fibroblast growth factor family
5. Hepatocyte growth factor
6. Insulin like growth factor (IGF) family: IGF-1 & 2.

**Death of Neuron:**

Excessive activation of excitatory amino acid receptors, excitotoxicity causes the neuronal cell death. Experimental model of stroke is associated with increased levels of glutamate in extracellular compartment and attenuation of neural damage by denervation of those nerves or using glutamate antagonist. The distribution of ischemia sensitive cells matches with that of NMDA receptors (except cerebellar purkinje cells). In global cerebral ischaemia, kainic acid and AMPA receptors are activated and their antagonism is protective. Hypoglycemia induced damage is also reduced by NMDA antagonists. Although, stimulation of extrasynaptic NMDA receptor mediate cell death while synaptic one is protective. Excitotoxicity leads to increased calcium influx, leading to activation of protein kinases, proteases, endonucleases, nitric oxide synthase and thereby metabolic dysfunction and free radical generation. Activation of poly-ADP-ribose polymerase, in response to free radical DNA damage, is also critical.

Apoptosis or programmed cell death is important for physiology and pathology. During embryogenesis, the neurons which fail to reach the target, get destroyed by this. The hallmark of apoptosis, DNA fragmentation is seen in variety of neurologic diseases. Mitochondria has essential role in apoptosis. The redistribution of cytochrome-c and apoptosis inducing factor (AIF) leads to activation of caspases. Caspase independent pathway occur after DNA damage.

**Stem Cells:**

It was previously thought that nervous tissue was non-mitotic one, especislly regarding the neurons. But that very idea has been challenged by the discovery of neural progenitor cells or stem cells in adult CNS, which are capable of differentiation, migration over long distances and extensive axonal arborization and synapse formation with specific target. So, there must be some factors which mediate this differentiation, growth, survival and migration. Once this is well understood, this knowledge can be exploited to use the stem cell in various therapeutic context. One advancement in this regard is development of induced pluripotent stem cells by treating adult somatic stem cells with4 pluripotency factors (SOX2, KLF4, cMYC, & Oct4). But the main challenge is generation of position and neurotransmitter specific neuron subtypes and to avoid the persistence presence of undifferentiated embryonic stem cells which are capable of forming tumor. Apart from these safety and ethics, particularly with the use of fetal tissue, is the concern.

**Genetic Basis of Neurological Diseases:**

Now-a-days many neurological and psychiatric diseases can be diagnosed by genetic testing. It is because of the fact that at least 350 disease causing gene have been detected in relation to various neurological diseases and more than 1000 neurological disorders have been mapped to different chromosomal locations. Most important examples include mutation of amyloid precursor protein, microtubule-associated protein tau (MAPT), α-synuclein in Alzheimer’s disease, fronto-temporal dementia and Parkinson’s disease respectively. Mutated gene leads to altered processing, thereby aggregation of protein leading to cell death. Genome-wide association studies (GWAS), based on “common disease, common variant” hypothesis, have been conducted to identify relatively common risk alleles in general population. More than 1000 have been carried out with different important finding like >50 risk alleles identified for multiple sclerosis. Bioinformatics tool are also being used to identify their biological role and their heterogeneity in population. Another revolution has been made in this field with the introduction of high throughput sequencing methodologies to identify different sequence variants as seen in whole genome sequencing in patient of Charcor-Marie-Tooth neuropathy to identify SH3TC2 gene mutations. Moreover, many of the diseases are caused by copy number variations of genes resulting from unequal crossing over. The first disease in this regard is Charcot-Marie-Tooth disease type 1a which was due to duplication of gene encoding myelin protein PMP22. This gene dose effect can be seen in some cases of Parkinson’s disease, Alzheimer’s disease, many behavioural phenotypes, learning disorders and autism spectrum disorders. Alternate splicing underlie the complexity and variation in nervous system affecting diferent important structures like neurotransmitter receptor and ion channels etc. Aberrant splicing is associated with Duchenne’s, myotonic, fascioscapulohumeral muscular dystrophy, ataxia telangiectasia, neurofibromatosis and fragile-X-syndrome. Epigenetics is the process by which gene expression can be regulated by postgenomic alteration in DNA or chromatin structure like DNA methylation, histone acetylation & methylation etc. Imprinting refers to epigenetic characteristic by which predominant expression of one allele is determined by its parental origin. Prader Willi syndrome, Angelman syndrome are the important examples. For studying pathogenesis and development of various therapeutic options, use of transgenic animal models is the example of application of current advances in molecular genetic techniques.

**Protein Aggregation and Neurological Diseases:**

Protein aggregation has been found to be pathogenic hall mark of neurodegenerative diseases. It is a matter of scientific debate that whether protein aggregate leads to neuronal death or it is only a secondary bystanders. Deposition of β amyloid is underlying pathogenic basis of Alzheimer’s disease. Mutant β amyloid with 42 amino acids instead of 40 in normal, has increased tendency to aggregate. Mutation in MAPT gene resulting in altered splicing of tau forming neurofibrillary tangle is seen in frontotemporal dementia. Huntington’s disease is associated with expansion of polyglutamate repeats. The protein aggregates or protein with polyglutamate expansion are toxic and they ubiquitinated for degradation but the cellular inability to do so leads to cellular dysfunction, impaired axonal transport and eventually cell death. Autophagy, the process of destruction of cytosolic components in lysosome, is associated with protein aggregate degradation and so implicated in many diseases. It seems to be impaired in Parkinson’s disease, Alzheimer’s disease, Huntington’s disease etc. Rapamycin which induces autophagy, has shown beneficial effect in transgenic mouse model of those diseases. In huntington’s disease, protein with polyglutamate expansion may bind with transcription factor and causes dysfunction leading to pathology. Another impact is chronic inflammation in many neurodegenerative diseases. It results from activation of Toll-like receptors (TLR) in response to pattern recognition signal from damaged or aging cells, which in turn occurs due to aggregated protein and heat shock proteins. Familial frontotemporal degeneration is due to the mutation in gene encoding progranulin, growth factor acting through tumor necrosis factor (TNF) receptors.

**Conclusion:**

The more we shall explore the biochemistry and molecular cell biology of nervous system, the more we shall understand the complexity of the same, the more we shall be able to understand the normal functioning of the system as well as the pathogenesis of various neurologic diseases. Then only, we can apply the knowledge to diagnose and treat those diseases effectively. Study of neurogenetics will help us to understand the inheritance pattern of the disorders. Intense research on the grey areas will shed more insights in future.

**References:**

1. Longo DL, Kasper DL, Jameson JL, Fauci AS, Hauser SL, et al. Harrison’s Principles of Internal Medicines. 18th ed. Vol. 2. New York. McGraw-Hill. 2012: 3092-3095.
2. Devlin TM. Textbook of Biochemistry with clinical correlation. 7th ed. Hoboken. John Wiley & Sons, Inc. 2011:1063-1098.
3. Krebs C, Weinberg J, Akesson E, Dilli E. Lipincott illustrated reviews:neuroscience. 1st South Asian Edition. New Delhi. Wolters Kluwer (India). 2020: 1-21.