APPLICATIONS OF NEUROCHEMISTRY

CHAPTER 1: INTRODUCTION TO NEUROCHEMISTRY AND NEURAL FUNCTIONS

1.1. Introduction

The study of neurochemicals is the focus of neurochemistry, a discipline of neuroscience. An organic substance that contributes to neuronal activity is known as a neurochemical. This phrase is frequently utilised to refer to neurotransmitters as well as other substances which alter neuron activity, like neuro-active medicines.

The roots of neurochemistry as a subject may be traced back to a sequence of "International Neurochemical Symposia," the 1st of which was titled *Biochemistry of the Developing Nervous System* and printed in 1954 (Brady et al., 2011). The *International Society for Neurochemistry* and the American Society for Neurochemistry was founded as a result of such sessions. The provisional nature of putative synaptic transmitter compounds like histamine, substance P, acetylcholine, and serotonin was debated at these initial sessions. By 1972, neurochemistry concepts had become more solid. Norepinephrine, dopamine, and serotonin are examples of neurochemicals classed as "putative neurotransmitters in some neuronal circuits in the brain."

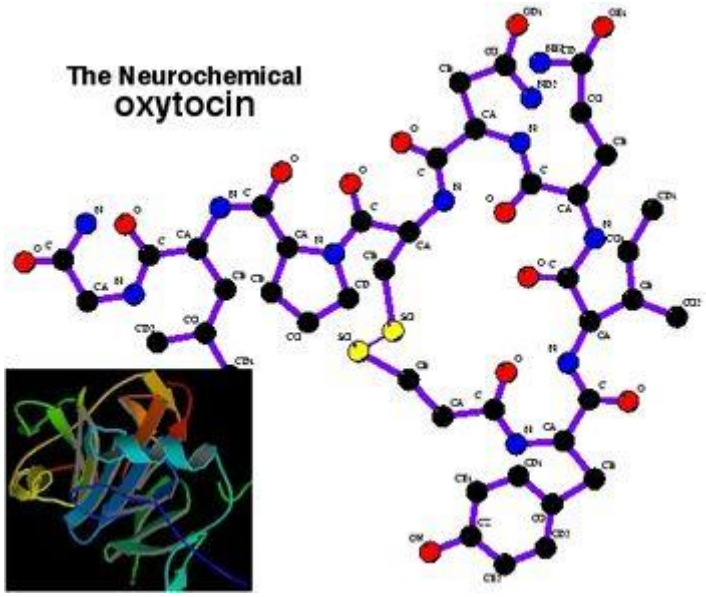

Figure 1.1. Neuropeptide oxytocin

Source: https://www.researchgate.net/figure/Figure-Chemical-structure-of-oxytocin_fig1_228413599

The following are some examples of neurochemicals:

1. Oxytocin has a role in maternal behaviour regulation. It is generated as a precursor protein inside magnocellular neurosecretory cells, which is then treated by proteolysis into its smaller active peptide state. Oxytocin is produced in certain areas of the brain, like the supraoptic

nucleus, and works on cells in the ventral pallidum to cause the behavioural impacts of oxytocin. The brain produces a substantial quantity of oxytocin that is carried to the posterior lobe of the pituitary & released into the bloodstream, where it reaches target organs like the mammary glands (milk letdown). In the figure inset, oxytocin is represented coupled to neurophysin, a carrier protein.

2. Despite being a gas, HNO_3 serves as a neurotransmitter. Since it's not liberated similarly to the other neurotransmitters, it's not grouped alongside them.
3. The most frequent neurotransmitter is glutamate. GABA or Glutamate is secreted by the majority of neurons. Glutamate is stimulating, which means that it triggers nearby cells to fire action potentials when it is released by a single cell. “It's worth noting that glutamate is chemically similar to the MSG often utilized in Chinese cooking”.
4. Serotonin regulates emotion, sleep, as well as other aspects of life.
5. A further instance of a neurotransmitter is dopamine. It is important for the limbic system that is involved in emotional function and regulation, to function properly.
6. A neurotransmitter known as GABA is an inhibitory neurotransmitter.
7. Acetylcholine is a neurotransmitter that helps with motor function.

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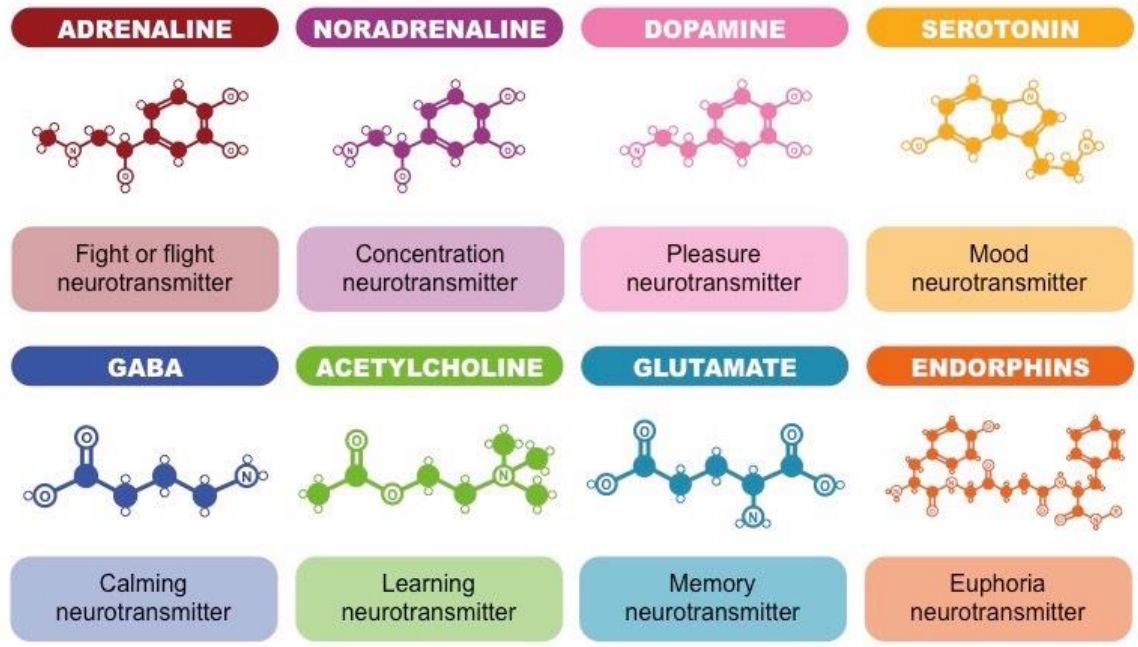

Figure 1.2. Kinds of neurotransmitters

Source: https://ib.bioninja.com.au/options/option-a-neurobiology-and/a5-neuropharmacology/types-of-neurotransmitters.html

Neurochemistry is a branch of science that studies the kinds, textures, and functioning of chemical elements present in the nervous setup (Heinbockel, 2018). These elements, in turn, control the neural system's physiology (Kandel et al., 2013). Little neurotransmitters, organic molecules, and neuropeptides are among the chemicals present in the nervous setup, and neurochemistry is involved with them. Neurological illnesses, such as Alzheimer's disease and Parkinson's disease, are frequently the result of abnormalities in the body's neurochemistry. Neurochemicals are used in medicine to change brain function and cure illnesses. Neurochemists look at how the elements of the nervous setup interact via procedures including learning, neural plasticity, development of the brain, and formation of memory, as well as how such elements alter as illness, brain malfunction, and ageing progress. The chemical constituents of the nervous system would be introduced in this part, along with a detailed discussion of how internally & externally influence and affect such constituents (Bear et al., 2009).

1.2. Building blocks of the nervous system

The nervous system is made up of a large number of cells that differ in shape, function, as well as how they react with one another. Nerve cells, often known as neurons & glial cells are the 2 main kinds of cells. Both categories have several subclasses, each of which is called depending on its shape or function. Neurons are classed as interneurons, motor, or sensory depending on their role in neural networks, or as uni-polar, bi-polar, multi-polar, or pseudounipolar depending upon their organisation & existence of axons or dendrites. Axons transport data to other sections of the nervous system, whereas dendrites are the receiving component of a nerve cell. In brain circuits, although, this difference may be obscured since both dendrites & axons may perform either role. Adult humans have axons that exceed a length of one and a half metres, while bigger animals like giraffes have much longer axons. Axons transfer physical substance toward the axonal terminus and from the terminus to the cell body, as well as serve as long-distance communication mechanisms for data through the transmission of action potentials. Protein synthesis takes place in the cell body, which also houses genetic data. As a result, all proteins as well as organelles like mitochondria which are required in the axon terminus must be transported down the axon via motor proteins. Dynein & kinesin, 2 motor proteins in the axon, transport vesicles or organelles across the microtubules.

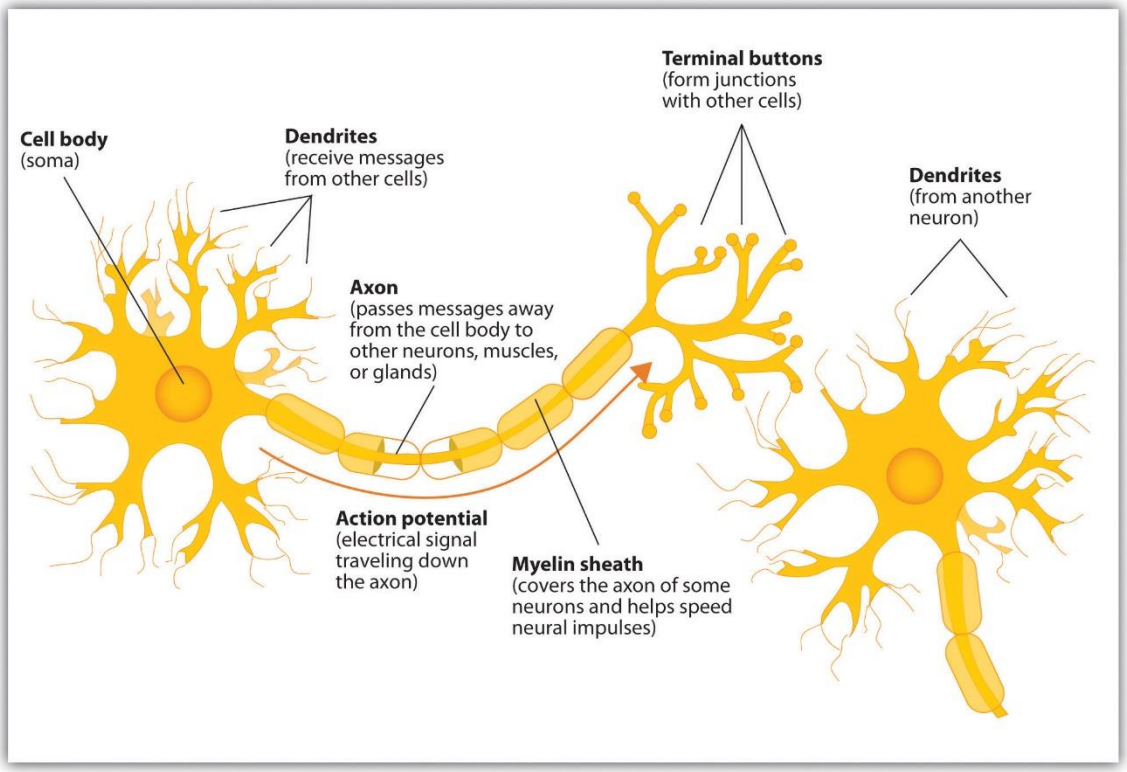

Figure 1.3. The nervous system's structure and components

Source:https://openpress.usask.ca/introductiontopsychology/chapter/the-neuron-is-the-building-block-of-the-nervous-system/

Kinesin transports vesicles from the endpoint to the cell body (movement of anterograde axonal), whereas dynein transports vesicles from the endpoint to the cell body (movement of retrograde axonal).

Glial cells are also available in a variety of flavours. Glial cells are becoming more well-known for their physiological roles in the nervous system, earning the moniker "true heroes of the nervous system" (Young, 2010). Myelin-forming Schwann cells & satellite cells are just discovered in the peripheral nervous system (PNS), whereas astrocytes (protoplasmic & fibrous), myelin-forming oligodendrocytes, and microglia are just discovered in the central nervous system(CNS). Although, these widely recognised categories, it must be obvious that nerve cells have such a wide range of morphology that it is nearly difficult to describe them accurately depending upon the shape, neurotransmitter makeup, ultra-structure, localization, or physiology. Moreover, neurons with comparable structure and function are reported in far-flung animal species without current evolutionary ties.

Nerve cells have the mitochondria, smooth & rougher endoplasmic reticulum, Golgi apparatus, nucleus, as well as other cellular components seen in many other cell kinds. The nucleolus & Nissl material in the cytoplasm are particularly intensely labelled when nerve cells are stained with dyes like cresyl violet toluidine blue (nucleic acid stain & Nissl staining) (Young & Baldwin, 2007). Bounded

ribosomes on the ER Unbounded ribosomes in the cytoplasm are referred to as Nissl substances. This dark staining appearance reflects nerve cells' intense metabolism and constant creation of proteins and peptides, indicating that they are amongst the body's highly active cells.

1.3. Channelopathies and excitable cell membranes

Membranes, which are made up of proteins & lipids, divide nerve cells as well as glial cells. Such proteins & lipids are essential for every neuron's specific functional involvement in the brain network, as well as the intracellular processes that take place in dendrites & axons far from the cell nucleus. Dendritic spine modification & axonal direction are moulded throughout development concerning signal input at localized membrane sections that is transmitted to the interior of the cell via particular pathways & receptors. The Interior and exterior of cellular membranes vary, allowing for an uneven work division due to an uneven division of proteins & lipids amongst axoplasmic & cytoplasmic leaflets (Xu et al., 2020). Lipids play a crucial role in the nervous system's function & structure. The membrane of lipids makes up the majority of the myelin that surrounds axons in both PNS and CNS. Membranes at the junctions, the linkages amongst nerve cells, contain distinct lipid contents. The connection has a synaptic apparatus comprising proteins & vesicles which assist in the specialized features of such membrane sections as well as synaptic plasticity (variation in synaptic propagation from pre-synaptic to post-synaptic neurons) (López et al., 2007). Lipid intermediates & lipid adjustment have a role in cell development signalling pathways, as well as influencing the function of trophic components and receptors (Heinbockel, 2017).

Nerve cells are stimulated cells with particular information-transmission characteristics. The membranes of the Nerve cell are designed with extremely critical pores or ion channels for Na, K, Ca, & Cl ions to do this. Such channels are essential for membrane stimulation and action potential transmission. Ion channels respond to voltage variations (channels of voltage-gated), chemical binding (channels of ligand-gated), and mechanical disruption.

Channelopathies, or ion channel diseases, are caused by impaired ion channel function as a result of abnormalities with subunits of the ion channel or having the control of the ion channels (Rose, 1998). When scientists discovered that mutations in a sodium channel subunit or a mutation in a gene that codes for a chloride channel in skeletal muscle resulted in hereditary muscle disorder, they called it "channelopathies." The field of channelopathies has developed massively since then, with more than 100 publications in the last five years (Shiang et al., 1993). Mutations in a glycine receptor subunit or a nicotinic acetylcholine receptor subunit have also been implicated in the development of channelopathies for ligand-gated ion channels (Steinlein et al., 1995). The main reasons for channelopathies may be found to be either hereditary reasons (such as congenital, arising from one or more mutations in the genes encoding the ion channel) or accumulated reasons (such as toxins, autoimmune invasion on an ion channel, etc.).

1.4. Neurotransmitters and neuropeptides

Neuropeptides & neurotransmitters are the most well-known neurochemicals because they can affect mind activity (Bear et al., 2009). One class of neurotransmitters is generated by ordinary amino acids like gamma-aminobutyric acid (GABA), glutamate, & glycine, which are all found in small amounts in the body. Such amino acids are involved in a variety of processes all across the body. These are packed and kept in synaptic/secretory vesicles in the nerve endpoints of neurons so that they may be discharged via exocytosis in a calcium-dependent way when the neuron fires. After each synaptic discharge cycle, the vesicular membrane is regenerated or endocytosed, to prepare for the next one (Argiolas & Melis, 1995; Werner & Covenas, 2010).

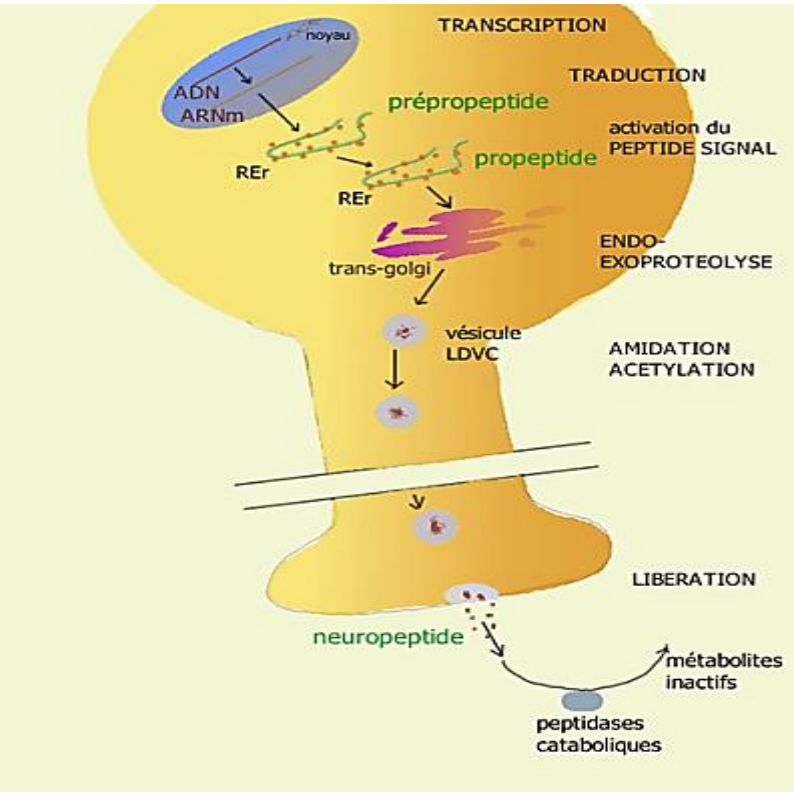

Figure 1.4. Neuropeptide production

Source: https://www.differencebetween.com/difference-between-neuropeptides-and-vs-neurotransmitters/

The very common excitable neurotransmitter is glutamate. It is emitted at excitable synapses, causing membrane potential depolarization and perhaps excitatory firing in the post-synaptic cell. GABA, on the other hand, is the most well-known inhibitory neuro-transmitter. Neuronal excitation is reduced due to its effect. Glycine, an inhibitory neurotransmitter present in the spinal cord, retina, and brain-stem is another inhibitory neurotransmitter. Monoamines are a class of neurotransmitters entailed in certain types of memory, excitation, sensory processing, & sentiments regulation (Bloom, 1984; Jacob & Nienborg, 2018). Medicines are utilised to modulate their impacts in individuals with mental and

neurological illnesses due to their functional responsibilities (Kurian et al., 2011). Monoamines have an amino group connected to an aromatic ring by a 2-carbon chain, as its name suggests. Monoamine oxidases are enzymes that stop monoamines from acting. Monoamines include epinephrine (adrenaline), dopamine, norepinephrine (noradrenaline), histamine, & serotonin. Because they include a catechol group, the first 3 are also referred to as catecholamines. Neurotransmitters are discovered as residual amines like tryptamine, octopamine, phenethylamine, tyramine, as well as others. Opioid peptides, substance P, somatostatin, cocaine & amphetamine-regulated transcript (CART), Oxytocin, orexin, neuropeptide S, glucagon, endorphin, dynorphin, neuropeptide Y, enkephalin, as well as other neuropeptides are examples of neuropeptides. Gaseous neurotransmitters include CO, nitrous oxide, & hydrogen sulphide (Burette et al., 2002). Such neurotransmitters are produced from scratch in nerve cells and can quickly permeate over the membrane of plasma to influence nearby cells due to their chemical makeup. To elicit skeletal muscle contraction, acetylcholine is produced in the autonomic nervous system as well as from motor neurons at the neuro-muscular endpoint. Acetylcholine is a chemical ester of choline & acetic acid. Since they are created from membrane lipids and are lipids, endogenously generated cannabinoids (endocannabinoids) like anandamide vary from the previously stated neuro-transmitters. They may be quickly generated on request from the cell membrane and delivered non-synaptically rather than synaptically, as with traditional neurotransmitters (Heinbockel et al., 2016 ; Harvey & Heinbockel, 2018). Endocannabinoids control presynaptic neurotransmitter discharge by binding to cannabinoid receptors on presynaptic neurons. -Endocannabinoids, along with gas neurotransmitters, are hence uncommon neurotransmitters (Barañano et al., 2001; Boehning & Snyder, 2003). The reality that all these new neurotransmitters serve as downstream mediators at synapses & pre-synaptically control whether GABAergic or glutamatergic synapses to modify discharge-probability in synaptic plasticity is one of their most notable features. Endo-cannabinoids & gaseous neurotransmitters are demonstrated to have a functional responsibility in experience-based activity and modulate a range of synaptic plasticity patterns (Cachope, 2012; Hardingham et al., 2013).

1.5. Variables that have an impact on neurochemistry

What are certain of the variables that have an impact on the chemistry of the nervous system? Sensory inputs, ambient signals like recreational drugs, medications, as well as poisons, and physical changes like ageing and disorder are all examples of variables that might alter neurochemistry & behaviour (Tiraboschi et al., 2004; Simpson & Kelly, 2011). Instances of these variables that are recognized to have an impact on neurochemistry are outlined and described in further depth further down this page. Please keep in mind that this listing is not complete and that, in principle, practically any environmental stimuli or internal condition might have an impact on neurochemistry (Castillo et al., 2012; Katona & Freund, 2012).

1.5.1. Sleep

Circadian rhythms, which are a neurochemical (& potentially epigenetic) foundation, regulate sleep. Numerous brain areas are involved while waking, including the basal forebrain, lateral & posterior hypothalamus, and tegmentum & pons nuclei. Monoamines & acetylcholine, glutamate, and orexin or hypocretin are neuro-transmitters that have a role in wakefulness. The anterior or preoptic hypothalamic region, on the other hand, governs dynamic sleep processes, and peptide & GABA factors such as developing hormone-discharging hormone, prolactin, & cytokines improve sleep . Adenosine is a key homeostatic component that acts on A1 & A2A receptors in the pre-optic & basal forebrain regions. Sleep deprivation induces adenosine discharge and restoration of sleep via increasing inactivating nitric oxide synthase in the basal forebrain. Several genes related to energy metabolism, neuronal propagation, synaptic plasticity, & stress defence are revealed to be differently regulated in sleep vs wakefulness (Stenberg, 2007).

1.5.2. Exercise

A significant study has currently been conducted into the neurochemical variation that happens after & during exercise, with the findings that it provokes the upsurge of several chemicals, which includes neurotrophins, cortisol, lactate, such as BDNF, VEGF, and IGF-1, neurotransmitters such as norepinephrine, serotonin, dopamine, glutamate & acetylcholine, and neuromodulators such as endocannabinoids Although, it must be highlighted that most of such modifications are proven peripherally, and there are still gaps in our understanding of wherein such variations happens in the brain. As a result, more research is required to establish a relationship between exercise-induced variations in peripheral levels and variations in central levels, as well as to determine how such substances are implicated in exercise-induced variations in cognitive, emotional, and other aspects of behaviour (Basso & Suzuki, 2017).

1.5.3. Diet

The scientific discipline of "nutritional neuroscience" is associated with the impact of diverse diet components like micro-nutrients & macro-nutrients including vitamins, minerals, food additives, and dietary supplements on neurochemistry. Nutrition is implicated in practically every facet of neurological function, influencing neurotrophic variables, neuronal networks, neurogenesis, & neuroplasticity, according to current studies on nutrition and its influence on the brain . This is unsurprising given that the brain utilizes a disproportionately big quantity of energy in comparison to the rest of the body. The human brain, for example, accounts for about two per cent of total body mass but consumes about twenty-five per cent of total energy input. As a result, systems included in the transport of energy from meals to neurons are expected to be critical for brain function regulation. Moreover, deficiencies in some vitamins as well as other co-factors, and the effects of metabolic

diseases like diabetes, impact memory by modifying procedures in the body linked with energy management and the formulation of neuroendocrine & neurotrophic variables (that is, IGF-1 & BDNF) as well as neurotransmitters in neurons, which may impact synaptic plasticity, neurotransmission, and cell growth (Dauncey, 2009).

1.5.4. Stress

Stress is characterized by body-brain integration to an environmental or internal provocation that the body interprets as a disruption in homeostasis. The limbic system's reaction to stress includes both the activity of multiple neurotransmitters as well as the responsiveness of neurons to hormones and other chemicals produced by the adrenal cortex, namely glucocorticoids. As a result, the body-brain reaction is likely to play a significant contribution in the response to stress (Mora et al., 2012). Severe stress is linked to changes in neurotransmitters including acetylcholine, dopamine, glutamate, and GABA in brain regions that control stress reactions. The amygdala, prefrontal cortex, hippocampus and nucleus accumbens are among such regions. Glucocorticoids also have a function in certain parts of the brain, interacting with various neurotransmitters. Neuro-modulators secreted from peripheral organs like the gonads (estrogens), pancreas (insulin), and liver (IGF-1) play a function as well. A long-term rise in glucocorticoid levels caused by a tough lifestyle might accelerate neuronal harm that happens in the aforementioned regions of the brain as people age. Stress depletion, on the other hand, can have an anti-ageing impact (Mora, 2013).

1.5.5. Meditation

Yoga & Meditation are two examples of stress-relieving techniques. Such strategies have lately gotten more curiosity as a result of a growing body of evidence demonstrating both indirect & direct effects . Depending upon previous research, it is shown that meditation modulates the levels of neurotransmitters including dopamine, GABA, norepinephrine, and serotonin in a manner that helps to alleviate psychological problems like anxiety. Meditation can also work as a sort of preventative medicine by lowering baseline levels of stress neurotransmitters & hormones (Krishnakumar et al., 2015).

1.5.6. Alcohol

Several neurotransmitters in the nervous system are affected by alcohol. Its main function is to promote GABA emission, and it does so primarily through GABAA receptors, resulting in sedative impacts (Banerjee, 2014). It also blocks postsynaptic NMDA excitable glutamate receptors, which adds to the sedative effect.

Furthermore, alcohol provides euphoric impacts, which are more closely linked to dopamine surges. Dopamine's impacts are also suggested to have a role in alcohol desire & relapse. Alcohol also affects

opioid receptors, which might result in the release of β-endorphins. Enhanced serotonin and reduced nicotinic acetylcholine receptors are two other key impacts .

1.5.7. Recreational drugs

Medications may interfere with neurochemicals' normal functioning, hinder how they should operate, or impair their propagation (Korpi et al., 2015). Pleasure is frequently boosted initially, while intellectual capacity & reason are generally reduced. Psychomotor stimulants such as amphetamines, methamphetamines, and cocaine affect an excess supply of neurotransmitters, primarily the norepinephrine and the monoamines dopamine, and can also inhibit them from being absorbed back, resulting in an unusually substantial quantity of norepinephrine & dopamine in synapses, activating the mesolimbic dopamine setup (Hill & Thomas, 2011; Antoniou & Tseng, 2002). Medicines such as ecstasy (3,4-methylenedioxymethamphetamine) disrupt serotonin propagation and transit through brain circuits in the same fashion. Other drugs, like opioids, marijuana, & heroin behave as activating neurons, agonists, and interrupting the natural propagation and generation of neurotransmitters. They mimic endogenous brain chemicals as well as bind to receptors as activating neurons, agonists, interrupting the natural propagation and generation of neurotransmitters. The brain may be reconfigured by neuroplasticity as it seeks to sustain chemical homeostasis after recurrent drug misuse (Enevoldson, 2004).

1.5.8. Neurodegenerative diseases and ageing

Neurobiology of ageing research is starting to reveal the processes that underpin not just the physiology of brain ageing, as well as the mechanisms that render people more prone to cognitive impairment and neurodegenerative illnesses (Hung et al., 2010; Walker et al., 2019).The impairment of neurotransmission in age-associated illnesses including Alzheimer's & Parkinson's disorder has sparked research into the neurochemistry of the ageing human brain. Age-associated alterations in the cholinergic, serotonergic, and dopaminergic systems are the most consistently identified of all the neurotransmitter setups investigated (Strong, 1998). The dopamine system, particularly, is prone to deterioration with age (Dreher et al., 2008). The link between these neurotransmitters and emotion, cognition, and motor function can play a role in age-associated behavioural variation and predisposition to age-associated disorders (Pereira et al., 2012; Hou et al., 2019). Furthermore, abnormalities in certain neurochemical systems and other pathophysiologic procedures can interact to cause age-associated neurodegenerative disorders (Leshner & Koob, 1999).

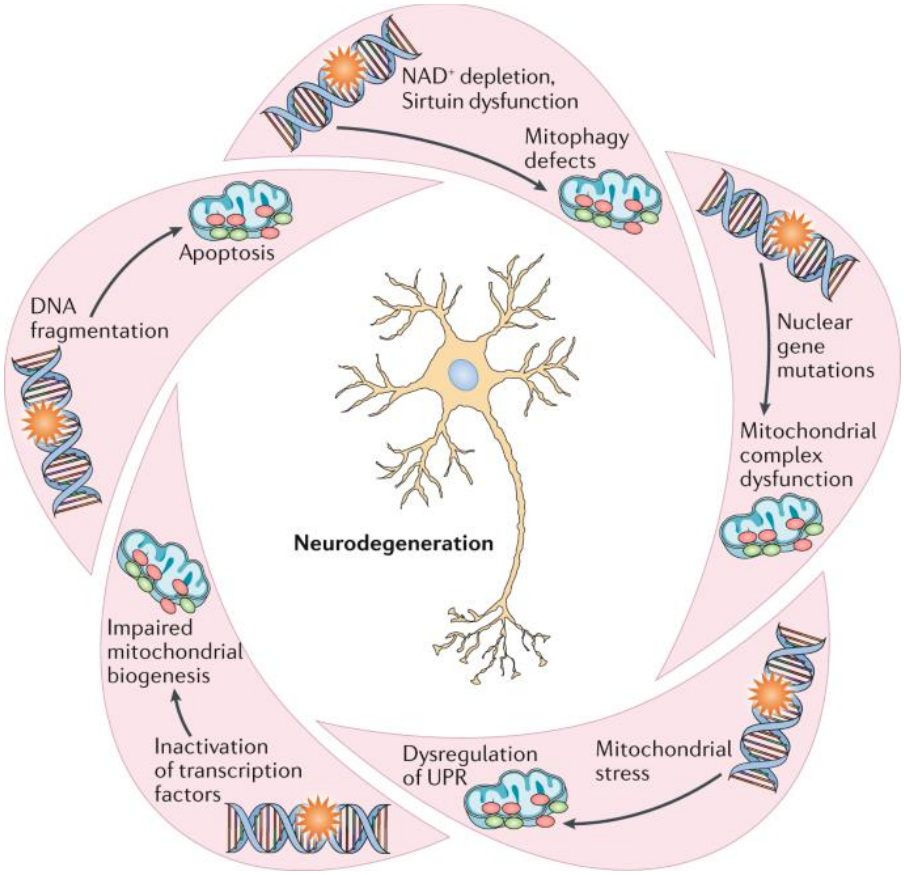

Figure 1.5. Neurodegenerative ageing procedure

Source: https://www.nature.com/articles/s41582-019-0244-7