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THE THERAPEUTIC AND PATHOLOGIC BASES OF NEUROLOGIC DISORDERS REST ON CNS TRANSMISTERS:-

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ABSTRACT

Therapeutic connotes treatment or management of a disease or disorder while pathologic connotes causative and, or processes of a disease or disorder. Central nervous system (CNS) transmitters are biologic molecules, neuronal or extraneuronal that are involved in the transmission or modulation of signals from one neuron to the other or from neuron to an effecter cell or tissue in order to effect an action in the brain. The action could be excitatory or inhibitory. CNS transmitters can broadly be sub-classified into three based on their site of production and actions in the brain. These are **Neurotransmitters** that are produced in the neuron, stored in the vesicles, destroyed in the neuron and could act as fast or slow transmitters. Examples of which include glutamate, aspartate, gamma amino butyric acid(GABA), dopamine, acetylcholine, serotonin, histamine, adrenaline and noradrenalin. **Neuromodulators** that may be produced in the neuron, may be destroyed in the neuron and act predominantly as slow transmitters. A single Neuromodulator may speed up the action of a slow Neurotransmitter, modify the action of a fast Neurotransmitter or combine with another modulator to effect a brain action. Examples of which include purines, pyrimindes, prostaglandins, nitric oxide, hydrogen sulphide and some second messengers. **Neurotrophic factors** that are neither produced nor destroyed in the neurons and are essentially involved in neuronal gene remodeling. Strictly, speaking they are not CNS transmitters but, are essential in transmission. They include substance-P, enkaphalins, endorphins and the host varieties of growth factors cum derived growth factors. Diseases or disorders like seizures/convulsions, Parkinsonism, Alzheimer's, Depressions, Mania, Anxiety, Hypertensions, schizophrenia, autism, huntington's disease, tardive dyskinesia, myasthenia gravis, among others are mediated by one CNS transmitter or the other. Theories in CNS like Mono Amine theory of Affective disorders and Dopamine theory of Schizophrenia implies the classical antidepressants and classical antipsychotics obeying these theories respectively in their mechanisms of actions. Benzodiazepines, relieve anxiety via their actions on GABA. Anxiety is also relieved by buspirone, gepirone and ipsapirone via their effects on serotonine (precisely $5HT1_A$). Alpha $_2$ methyldopa, Resapine, Clonidine, Prazocine etc bring down high blood pressure via their actions on adrenaline/noradrenaline. Levodopa, Carbidopa, Entacapone, Tolcapone, Selegelline etc bring relieve in Parkinsonism via actions on dopamine. **Conclusions**: From afore going and several other numerous instances, one can clearly conclude that CNS transmitters play very crucial roles in mediation of neurological diseases and also form the bedrock in the drug management of these disorders. A clear understanding of CNS transmission is thus sine qua nom to a good management of neurological diseases/disorders.

KEYWORDS: Neurological diseases/disorders, CNS transmitters, Alzheimer and food additives, Pathogenesis, Drugs treatment of CNS disorders.

INTRODUCTION

Central nervous system (CNS) transmitters are biologic molecules, neuronal or extraneuronal that are involved in the transmission or modulation of signals from one neuron to the other or from neuron to an effecter cell or tissue in order to effect an action in the brain. The action could be excitatory or inhibitory. CNS transmitters can broadly be sub-classified into three based on their site of production and actions in the brain.

These are **Neurotransmitters** that are produced in the neuron, stored in the vesicles, destroyed in the neuron and could act as fast or slow transmitters. Examples of which include glutamate, aspartate, gamma amino butyric acid (GABA), dopamine, acetylcholine, serotonin, histamine, adrenaline and noradrenalin.

Neurotransmitters (NTs) are often referred to as the body's chemical messengers. They are the molecules used by the nervous system to transmit messages between neurons or from neurons to tissues. Communication between two neurons happens in the synaptic cleft or gap. Here electrical signals that have travelled along the axon are briefly converted into chemical ones through the release of neurotransmitters, causing a specific response in the receiving neuron (Demeter and Starter, 2012).

A neurotransmitter influences a neuron in two ways; it can be either excitatory or inhibitory. An excitatory neurotransmitter promotes the generation of an electrical signal called an action potential in the postsynaptic neuron while an inhibitory neurotransmitter blocks the neurotransmitter action within the central nervous system, which consists of the brain and the spinal cord. Neurotransmitter passes from neuron to neuron. In the peripheral nervous system, which is made up of the nerves that run from the spinal cord to the rest of the body, the chemical signals pass between neuron and adjacent muscles or glands which they innervate. The first neurotransmitter, acetylcholine was discovered in 1921 by a German Pharmacologist Otto Loewi (Suppa and Papazachariadis, 2012).

The amino acids that serve as neurotransmitters include glycine, glutamate, aspartate, gamma-amino butyric acid (GABA), among others. Glutamate is the most abundant excitatory neurotransmitter in the central nervous system especially in the cerebral cortex. GABA on the other hand, is the most abundant inhibitory neurotransmitter in the central nervous system particularly the cerebral cortex which is largely responsible for such higher brain functions as thought and sensational interpretation.

The second family is the amines. Among the amine neurotransmitters are dopamine, histamine, norepinephrine and serotonin. Dopamine is involved in the movement of muscles, reward, motivation and it controls the secretion of the pituitary hormone, prolactin, which triggers milk production in nursing mothers (Demeter and Starter, 2012). On the other hand, serotonin is involved in functions such as sleep, memory, appetite and mood. Norepiephrine is the main neurotransmitter in the sympathetic system where it is involved in the control of blood pressure, heart rate and many others. Acetylcholine plays a role in both peripheral and central nervous systems where it is involved in memory, learning and movement. The third neurotransmitter family is the peptides. Peptide neurotransmitters are poorly understood, but scientists know that peptide neurotransmitter called substance p influences the sensation of pains. Neurotransmitters are synthesized from precursor compounds such as amino acids, peptides and the dietary amine called choline (Demeter and Starter, 2012)

Neuromodulators that may be produced in the neuron, may be destroyed in the neuron and act predominantly as slow transmitters. A single Neuromodulator may speed up the action of a slow transmitter, modify the action of a fast transmitter or combine with another modulator to effect a brain action. Examples of which include purines, pyrimindes, prostaglandins, nitric oxide, hydrogen sulphide and some second messengers.

Neurotrophic factors that are neither produced nor destroyed in the neurons and are essentially involved in neuronal gene remodeling. Strictly, speaking they are not CNS transmitters but, are essential in transmission. They include substance-P, enkaphalins, endorphins and the host varieties of growth factors cum derived growth factors.

CNS Transmitters, disorders and Drug treatment

Dopamine, Parkinsonism and Schizophrenia:- Dopamine is a major inhibitory neurotransmitter that has both peripheral and central effects. Dopamine plays essential roles in Parkinson's disease and psychosis. There are four principal pathways of dopamine namely: Nigrostriatal that modulates voluntary movement, Mesolimbic that modulates emotions and rewards, giving dopamine its name as "Reward neurotransmitter", Mesocortical that modulates behavours and inhibitions and finally the Endocrine (Tuberohypophyseal) pathway that regulates emesis and prolactin secretions. Peripherally, dopamine is a more potent vasoconstrictor than adrenaline. Dopamine is also good in management of renal disorders as dopamine at low dose stimulates diuretic effects on the papillary muscles of the kidneys. It has stimulant effect on the heart muscles thus very good in management of cardiovascular collapse. The major drawback in the use of dopamine and its agonist like bromocriptin, is emesis which is a major reason why dobutamine may be preferred in management of cardiovascular collapse.

The dopamine hypothesis of schizophrenia posits that increased subcortical dopamine underpins psychosis. *In vivo* imaging studies indicate an increased presynaptic dopamine synthesis capacity in striatal terminals and cell bodies in the midbrain in schizophrenia (Purves-Tyson et al., 2017)

Subcortical dopamine dysregulation is considered the final common pathway in the pathophysiology of schizophrenia. The dopamine hypothesis of schizophrenia was proposed, in part, based on the amelioration of symptoms by dopamine receptor D2 (DRD2) blockade, the main mechanism of action common to classical antipsychotic drugs. A current

version of the dopamine hypothesis posits that striatal hyperdopaminergia contributes to positive symptoms, and frontal cortical hypodopaminergia contributes to negative symptoms and cognitive deficits (Tiago et al., 2017; Purves-Tyson et al., 2017). Non selectivity of dopamine blockade in the various dopamine pathways accounts for the diverse adverse effects by classical antipsychotics.

Acetylcholine, Alzheimer, Asthma, PUD and Spasticity:- Acetylcholine is a major neurotransmitter. It is essentially excitatory in its actions. Acts via two major receptors, nicotinic and muscarinic. While nicotinic innervates the skeletal tissues/organs, the muscarinic innervates the smooth muscles/organs. Acetylcholine has three main physiologic activities, namely contractions cum mobilization of skeletal muscles. This function in excess results in spasticity which is normally balanced up by gamma amino butyric acid (GABA). Gabaergic drugs can thus be used as centrally acting skeletal muscle relaxants. Acetylcholine is a glandular stimulator, causing secretion of the fundus glands which in excess results in peptic ulcers disease (PUD). Anticholinergics thus are essential in management of PUD. It causes salivation which could result in nuisance during anaesthesia and surgery. Atropine and other anticholinergics are thus employed. Its constricting effects on the bronchial tree mediates asthmatic crisis that is handled with ipratropium. All physiologic actions above can be termed "Peripheral actions".

The major central action of acetylcholine is related to its cortical stimulation of memory and learning. Acetylcholine is chiefly found in the Ren Shaw cells of the brain and CT scan evidence of cortical destruction results in dementia as seen in Alzheimer, vascular dementia, Lewi body dementia etc. Drugs like tacrine, Neostigmin and physiostigmine are handy along this path of lo9gic.

GABA, Anxiety, Insomnia, Epilepsy and Huntington:- Gamma amino butyric acid (GABA) is a major fast inhibitory neurotransmitter. Gaba appears to be the only neurotransmitter that produced only in the brain. Glycine is an amino acid, produced in the spinal cord and functions like Gaba but, slow in action. Gaba receptors are broadly divided into Gaba-A and Gaba-B. Most clinically relevant actions of Gaba are via Gaba-A receptors. Actions of Gaba-A lead to decrease in cAMP leading to neuronal inhibition (hypnosis, Sedation, Amnesia) while actions of Gaba-B receptor lead to excitation via increase in cAMP. Actions, that mimic those of glutamate; thus balancing the actions of the human's brain. Gaba physiologically, balances the actions of acetylcholine (relaxation of skeletal muscles/Amnesia) and glutamate (Anticonvulsants and antiinsomnia). Gabaergic drugs include Gaba enhancers like Benzodiazepines, Barbiturates and Alcohols; Gaba analogue like gabapenten, Gaba hydrolysis inhibitors like Viagabatrin. Allosterism is the main mechanism of action of all Gaba enhancers while analogue, agonist and hydrolysis inhibitors act as their names connote.

Noradrenalin/Adrenaline, Depression, Mania and Hypertension:- Adrenaline and noradrenalin share common functions in humans/animals. They are interchangeably produced in-vivo. Clinically, adrenaline is available for use in man while noradrenalin may be used in animals.

Adrenaline peripherally, plays a major vasoconstrictor action to the major vessels but, dilates veinules/artrioles to facilitate sweating. Adrenaline is clinically very relevant in management of cardiovascular shock, allergy and septic shocks. Disorders in excessive production like in Cushing's syndrome, pheocromocytoemia or excessive physiologic action results in hypertension.

Centrally, adrenaline has mainly excitatory but, rarely inhibitory effects. Noradrenalin shares in the pathogenesis of hypertension where drugs like alpha 2 methyl dopa, clonidine, prazocin etc go on to demonstrate the relationship. Noradrenalin also obeys the mono amine theory of affective disorder as disordered decrease in its neuro-levels results in depression while in its disordered increase in neuro-level results in mania.

Glutamate, Epilepsy and Alzheimer:- Glutamate is a naturally occurring amino acid that is produced both centrally and peripherally. Glutamate also occurs naturally in many foods and seasonings as sodium monoglutamate (Sodium salt of glutamic acid) (MSG). MSG is made from fermented starch or sugar. Glutamate is used by virtually all living beings as a precursor in protein synthesis. Glutamate is interchangeably produced with GABA thus glutamate regulates biosynthesis of GABA via Gaba-hydroxylase. Centrally, glutamate is the most abundant excitatory neurotransmitter. It is stored in vesicles and released via presynaptic cells. Glutamate has two major groups of G-proteins coupled receptors-Ionotropic (results in direct release of ions once stimulated) and metaboric (Metabotropic- involved in metabolism, thus involved in non direct release of ions but, activates second messengers release once stimulated). The postsynaptic actions of glutamate via the NMDA or AMPA receptors are involved in memory and learning, wakefulness and alertness. Most clinically relevant effects of glutamate are via the NMDA receptors. Excessive secretion and, or activities may be seen in some gliomas or other neuronal tumors. Glutamate is physiologically regulated by GABA as well as dopamine. In dopamine theory of schizophrenia, dopamine excess production results in glutamate depletion to bring about disordered thought. One of the adverse effects of memantine, a glutamate antagonist is also psychosis. Glutamate when in excess could lead to euphoria to seizures/convulsions and finally to excitoneurotoxicity that results in hastened apoptosis. Apoptotic death of several cortical cells eventually results in dementia as seen in Alzheimer (Revett *et al*.,

2013). Glutamate is a non essential amino acid as the body synthesizes its needs thus excessive consumption via food additives may indeed be implicated in increasing incidences of Alzheimer's disease and other forms of dementia. Lamotrigine and memantine and good glutamate antagonists used in treatment of seizure and dementia respectively to buttress the above actions of glutamate.

Serotonin; Emesis, Pains, Depressions and Mania

Serotonin, also called **5-hydroxytryptamine**(5-HT), Enteramine, Thrombocytin -3-beta-Aminoethyl-5-hydroxyindole or Thrombotonin is an amine neurotransmitter with a wide range of somehow opposing actions via a diverse range of receptors. Indoleamine addition to tryptophan via hydroxylation produces 5-hydroxytryptophan which is decarboxylated to produce serotonin.

Serotonin has been referred to as entric-neurotransmitter because it's chiefly (90%) produced by the enterochromaffin cells of the myenteric plexuses. Serotonin is taken up by platelets while in blood circulation. Platelets on the other hand release serotonin during haemostasis. Serotonin will directly cause increased platelets aggregation. Vasoconstriction is caused to decrease blood loss but, vasodilation during fibrinolysis to encourage wound healing. Both opposing actions are via effects on endothelia cells. Serotonin stimulation of endothelin will cause vasoconstriction while that on nitric oxide will cause vasodilation. Serotonin may also potentiate the vasoconstrictive effects of angiotensin II and adrenaline to cause vasoconstriction, Serotonin also causes increase in GIT motility thus hastens blood transportation of serotonin via the enterohepatic circulation. Serotonin induces emesis via 5-HT_3 receptors. These above physiologic actions are essentially peripheral.

In the CNS, about 8% of serotonin is produced essentially by the Raphe cells. Serotonin mediates pains, anxiety, mood, sexual, emotional and other resources drives. Receptors of serotonin abound but, basically grouped 1-7. Groups 1 and 2 are further subdivided into A,B,C,D, E and F with diverse actions. Most serotonin receptors that are involved in central actions (1,2,4,5.6 and 7) are G-proteins coupled and membrane located. The only exception being the 5-HT_3 that is a ligan gated ion channel receptor. A wide range of drugs have effects on serotonin. They include those block reuptake like SSRi, TCA and MAOi. 5-HT1A agonist as anxiolytics eg buspirone and gapepirone. Those that block 5-HT_3, like granisetron and ondasetron and used as antiemetics especially, in chemotherapy.

Histamine, Inflammation, Seizures

Histamine is produced from histidine. Histamine is an autocoid like serotonin and prostaglandin. Histamine is an organic nitrogenous compound and involved in many physiologic functions, inflammation and as a neurotransmitter in the CNS. There are about four subtypes of histamine receptors (H 1-4). H_1 is located in the brain and skin and involved in the pathogenesis of itching, wakefulness and anorexia. Drugs that block H_1 cause sedation and norexia. Histamine receptors are G-proteins coupled receptors. Centrally, histamine receptors (H1,3 and 4) are richly found as projections from the histaminergic neurons of the mammalian hypothalamus (Tuberomammilary pathway). Peripherally, histamine is stored in mast cells and involved in immune response as well as allergy. It's involved in the pathogenesis of morning /motion sickness as well as asthma. Thus anti histamine receptor (H_1) and mast cells stabilizer eg sodium cromoglycate play pivotal role.

Histamine causes increase in vascular permeability thus vasodilation, hypotension, swelling (Wheals), anaphylactic shock, increase in erection, increase in glandular secretion eg H_2 on the parietal cells, seizures inhibition, increase in memory and learning, sneezing and runny nose as well as influence on multiple sclerosis and schizophrenia (Jadidi-Niaragh and Mirshafiey, 2010, Ifezulike *et al*., 2014).

Prostaglandins and epileptogenesis

Prostaglandins are a wide group of lipids biologic substances. They are involved in wide range of biologic activities in human, animals and even plants. They could be produced naturally from phospholipids or during inflammations. Phospholipids are acted upon by phospholipase A2 breaking them down to arachidonic acid which in turn is broken down to prostaglandins by the actions of cyclo-oxygenase. There are two isoforms of cyclooxygenase-the constitutive and inflammatory subtypes. While the constitutive brings about production of naturally occurring prostaglandin that is involved in mucosal protection in the gastrointestinal tract as well as uterine contractions or vascular smooth relaxation, the inflammatory causes inflammation. Inflammation causes pains, swellings, increase in temperature, redness and loss of functions. It could lead also to anaphylaxis. Misoprostol which a prostaglandin analogue, is a good oxytocic. NSAIDS and so many other analgesics block prostaglandins production via inhibition of cyclo-oxygenase (Azikiwe *et al*., 2014).

Centrally prostaglandin acts as neuromodulator and has been shown to increase seizure latency period as well as severity. Prostaglandin may therefore be incriminated in epileptogenesis. (Azikiwe et al., 2012).

CONCLUSIONS

From afore going and several other numerous instances, one can clearly conclude that CNS transmitters play very crucial roles in mediation of neurological diseases and also form the bedrock in the drug management of these disorders. A clear understanding of CNS transmission is thus sine qua nom to a good management of neurological diseases/disorders.

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