Neurochemistry of Neurochemicals: Messengers of Brain Functions

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Abstract: Neurochemistry refers to the chemical processes that occur in the brain and nervous system. This section of study determines how neurochemicals influence the network of neural operation. The brain transfers numerous chemical information via neurons to communicate. The main role of neurochemistry activities takes place in the brain, which allows it to perform numerous actions. Foundation of brain is a little bit different from man to man and several things can play a role in the levels of various neurotransmitters in the brain. It is supposed that differences in brain chemistry may accountable for a variety of behavioral disorders. A particular cell called neurons is the basis of brain. Neurotransmitters have the capability that it can trigger when ordered to do so, along with receptors for specific neurotransmitters. By sending messages with neurotransmitters to signal various cell activities, brain perform its functions. Neurotransmitter spreads chemical messages from neuron to neuron to broadcast certain work and thus it works. A neuron may accept many chemical messages, both positive and negative from the other neurons contiguous it. They are accountable to get the neuron to reply in different ways, or they may work combine to produce a certain effect. Since all of this occurs just within a split second, the neurotransmitter must be cleared away rapidly so that the same receptors can be activated again and again. Psychoactive drugs work by briefly influencing a man's neurochemistry, which thusly causes changes in a man's mind-set, cognition, perception and behavior. Neuropeptides are endogenous protein molecules that are utilized for neuronal signaling. These molecules exert more prolonged and diverse effects on behavior than neurotransmitters. Therefore the objective of this appraisal is to show study of the brain's chemical makeup especially neurotransmitters, psychopharmaceuticals, neuropeptides and their activities to nervous tissue.

Keywords: Neurochemistry, Neurochemicals, Messengers, Neurotransmitters, Psychopharmaceuticals, Neuropeptides, Brain Functions.

INTRODUCTION

Neurochemistry is the study of neurochemicals, including neurotransmitters and other molecules such as psychopharmaceuticals and neuropeptides that influence the function of neurons [1]. This special branch considers the impact of neurochemicals to the operation of neurons, synapses and neural networks. Neurochemistry enables the brain to work with the use of chemicals known as neurotransmitters [2]. Neurochemistry varies individual to individual which owing the variations of the neurotransmitters. Different environmental incidents can actively influence the levels of neurotransmitters and their receptors in the brain, as can factors like diet, medications and various drugs. Few chemical compounds and drugs have long term affects. In pregnancy, nursing, and mother-infant attachment neurochemicals have roles which cannot be ignored [3]. Dopamine which is a specific type of neurotransmitter found to be heavily interrelated with nicotine [4]. These can cause behavioral malfunctions in the way brain works, for example individuals who smoke create addiction to compounds like cigarettes because of the path in which nicotine changes brain chemistry. Neurotransmitters actively regulated various

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organic compounds in the nervous system and their activities in different biological processes [5].

In brain these chemicals are formed and through blood circulation these neurochemicals are transported within the brain [6]. For maintaining various events within the nervous system these chemicals required specific enzymatic action, metabolism, neural communication and other mechanisms. Any changes of electrophysiological activity of neurochemicals can be responsible for changing in the brain and behavioral conditions [7]. Neurons are used by the neurotransmitter for exchanging electro-chemical signals within the brain and thus help to make communication with other organs of body [8]. Neurochemicals are responsible for performing different cognitive, physical and mental performance, such as sleep cycle, pain response and our mental activities [9].

Neurotransmitters play a vital role in controlling the transmission of messages across the synapses to the receptors [10]. Neurotransmitters can have an inhibitory, or slowing down effect or an excitatory, or speeding up effect [11]. Neurotransmitters are imperative for memory, learning and behavior among other things. Factors such as foods affect these chemicals actions. Specific receptors on the postsynaptic membrane are the binding site for neurotransmitters [12]. There are various sorts of receptors for various neurotransmitters. This alteration in the electrical state of the postsynaptic cell may either excitatory or inhibitory. The action can be influenced by glial cells, which eliminate neurotransmitters from the synaptic cleft [13, 14].

Neuropeptides are also known as messenger molecules that carry message between neurons in the brain [15, 16]. In the mammalian brain, there are different neuropeptides. Hypothalamus is one of the main organs in body that discharge these chemicals and some are secreted into the blood, with peripheral outcomes as endocrine hormones [17]. Oxytocin neurons are good model system for revealing important aspects of many neuronal functions, comprising neuropeptide release. Peptides are more potent than other neurotransmitters. They need tiny amounts to yield an effect [18]. Peptides hormones found in neural tissue act as neurotransmitters and control numerous functions. For example, gastrin, that stimulates hydrochloric acid and intestinal motility [19]. Receptors in digestive tract and other neuropeptides are responsible for digestions [20]. Oxytocin and vasopressin are produced in the hypothalamus with receptors situated primarily in the brain. They have been connected with the memory and with the development of social attachments [21].

The research suggests that insufficiency, imbalances, and malfunctioning of neurotransmitters is extremely common in our society and they are accountable for numerous health complications, because when neurotransmitters are not dynamic appropriately then the mind and body do not connect effectively [22]. At the point when communication breakdowns, then organ systems don't function as they should. This outcome in an assortment of undesirable side effects both physically and mentally. The numbers of people suffering from some form of neurotransmitter imbalance are increasing [23]. Various factors for example, stress, diet, genetics and disclosure to toxins such as alcohol and nicotine are liable for this imbalance. This imbalance may progress thoughtful mental health complaints. It is observed that serotonin (5-HT) is linked with depression and anxiety disorders for example obsessive-compulsive disorder [24]. Norepinephrine may responsible for disease like schizophrenia, while too little can cause depressive symptoms [25].

To comprehend the chemistry of brain and the nervous system is one of the most complex dares for modern science. The human brain contains about 100 billion neurons and it has been estimated that these neurons form close to 10000 billion synapses. Therefore, the intention of this appraisal is to show the neurochemistry of chemical messengers predominantly neurotransmitters, psychopharmaceuticals, neuropeptides and their brain functions.

NEUROTRANSMITTERS

Neurotransmitters or chemical messengers are endogenous chemicals which allow neurotransmission [26]. They transfer signals over a chemical synapse, for example, a neuromuscular junction, starting with one neuron then onto the next target neuron, muscle cell, or gland cell [27]. Receptors of the target cells predominantly receive the neurotransmitters, which are released in synapses into the synaptic cleft from the synaptic vesicles [28]. Amino acids are the precursors which are required to synthesize neurotransmitters. These amino acids are abundantly found in the diet and require only few biosynthetic steps to be converted to neurotransmitters. In general, on daily basis, neurotransmitters play crucial roles in a wide range of

physiological processes and to maintain homeostasis [29]. The exact number of neurotransmitters are still unknown, however over 100 chemical messengers have been exclusively identified [26].

Classes of Neurotransmitters

Although neurotransmitters can be generally classified into two categories: excitatory and inhibitory [30], however some neurotransmitters are designated as both. In most of the cases, neurotransmitters directly activate one or more types of receptors. The effects on the postsynaptic cells are largely dependent on the properties of the receptors. Predominantly, most of the significant receptors have excitatory effects and these effects are largely dependent on some neurotransmitters like glutamate which upsurge the probability of the target cell to fire an action potential. On the other hand, for neurotransmitters like γ-aminobutyric acid (GABA), the main receptors all have inhibitory effects. In contrast, some neurotransmitters including acetylcholine can bind with both excitatory and inhibitory receptors. However, there are certain types of receptors that stimulate complex metabolic pathways in the postsynaptic cell to exert effects that cannot specifically be referred either as excitatory or inhibitory [27-33].

Excitatory Neurotransmitters

Excitatory neurotransmitters are also denoted as "on switches" of the nervous system, since they increase the probability of nerve cells to produce an action potential [31]. Excitatory neurotransmitters stimulate the excitability of cells by directly opening the ion channels including glutamate or by signal transduction pathways. These neurotransmitters play key role in maintaining body's most important and basic functions like, body's responses in emergency conditions, thinking processes, motor movement and critical thinking [32]. Physiologically, excitatory neurotransmitters including acetylcholine, epinephrine, norepinephrine, dopamine, histamine and glutamate help to uphold body's stimulatory effects like enhanced alertness, energy, and activity [26].

Inhibitory Neurotransmitters

Conversely, inhibitory neurotransmitters are also called as the "off switches" of the nervous system, due to their ability to decrease the likelihood of nerve cells to fire an action potential [34]. In general, excitatory effects must be balanced with inhibitory effects in brain to ensure it is properly functioning. If excitatory effects predominate then effects like irritability, insomnia, restlessness and even seizures can be observed. Inhibitory system of the body can be compared with the brakes on a car, which slows down the excitatory system or effects. The inhibitory neurotransmitters are also referred as the body's natural tranquilizers due to their effects in inducing sleep, diminish aggression and promote calmness. Common examples of inhibitory neurotransmitters are dopamine, GABA, taurine, acetylcholine, glycine and 5-HT [26].

From the chemical point of view neurotransmitters are monoamines, amino acids and peptides. There are two main groups of neurotransmitters: classical neurotransmitters (Table **1**) that are synthesized in the nerve terminals and neuropeptides stated later [34].

Mechanism of Neurotransmitters

In general, neurotransmitters are stored in a synapse in synaptic vesicles located at the presynaptic side of the synapse [35]. The neurotransmitters must need to cross the synaptic cleft to bind with the target receptors located in the membrane on the postsynaptic side of the synapse [36]. Most of the neurotransmitters are about the size of a single amino acid. Nevertheless, there are also some neurotransmitters which are as large as proteins or peptides [37]. Typically, a released neurotransmitter stays in the synaptic cleft for a shorter period of time before being metabolized by the enzymes, reuptake into the presynaptic neuron or bound to a postsynaptic receptor [38]. However, these short-term exposures are generally adequate to trigger a postsynaptic response achieved through synaptic transmission [39].

A neurotransmitter can be released at the presynaptic terminal either in response to a threshold or graded electrical potential and low level "baseline" release also can also take place well without electrical stimulation [40]. Ultimately, the released neurotransmitter then move through the synapse to be recognized and to be bound with the receptors of postsynaptic neurons. This binding can either lead to inhibitory or excitatory effects. It is believed that the neurons are well connected to many more neurons and these neurons can fire if altogether the excitatory effects are greater than those of inhibitory effects. Eventually, it will generate a new action potential at its axon hillock to release neurotransmitters and to pass on to another neighboring neuron [41].

Table 1: A Number of Classical Neurotransmitters and their Precursors [34]

System	Transmitter	Precursor
Cholinergic	Acetylcholine	Choline + Acetylcoenzym A
Aminoacidergic	GABA	Glucose → Glutamate
	Aspartic acid	Glucose + Glutamine; Glutamate
	Glutamic Acid	Glucose + Glutamine; Aspartate
	Glycine	Serine
	Homocysteine	Cysteine → Cystine
Monoaminergic		
Catecholamines	Dopamine	Tyrosine → Dihydroxyphenylalanine → Dopamine
	Norepinephrine	Norepinephrine → Epinephrine
	Epinephrine	–
Indolamines	Tryptamine	–
	5-HT	Tryptophan → 5-Hydroxytryptophan
Others, related to amino acid	Histamine	Histidine
	Taurine	Cysteine → Cysteamine
Purinergic	Adenosine	–
	Adenosine diphosphate	–
	Adenosine monophosphate	–
	Adenosine triphosphate	–

Brain Neurotransmitter Systems

Certain types of neurotransmitters expressed by the neurons occasionally form distinct systems. Activation these systems affect large volumes of the brain which is known as volume transmission [42]. Most important neurotransmitter systems comprise the dopamine system, the cholinergic system, the noradrenaline system, the 5-HT system, etc. Throughout the brain, trace amines, predominantly through trace amine-associated receptor 1 (TAAR1) activation, have a substantial effect on neurotransmission in monoamine pathways [43, 44]. A brief comparison of these systems is represented in Table **2**.

Neurotransmitters Imbalance

Scientifically, there are no recognized norms for appropriate levels or balances of different neurotransmitters. In most cases at any given time, it is practically impossible to estimate levels of neurotransmitters in a brain or body. Neurotransmitters are found to control each other's release and the regulation of neurotransmitter release is crucial to maintain normal physiological processes and to stay healthy [54-58]. Whereas, many neurological diseases and disorders including Parkinson's disease (PD), insomnia, depression, ADHD, memory loss, anxiety, addictions, dramatic changes in weight and addictions may take place due to the imbalances in neurotransmitter systems [59]. Various factors including chronic physical or emotional distress, genetics and certain types of medications are the major contributors to changes in neurotransmitter system [60]. Table **3** represents the disorders linked with the imbalance of neurotransmitters.

PSYCHOACTIVE DRUGS

Chemical substances which can cause alterations in consciousness, perception, or mood are known as psychoactive drug, psychotropic or psychopharmaceutical [91]. These chemical substances can be used for recreational purpose (legally or illegally) or purposefully to alter individual's consciousness, or for ritual, spiritual purposes as entheogens (i.e. any psychoactive substance that induces a spiritual experience). Some psychoactive drugs containing therapeutic values are also prescribed by physicians and other associated health care professionals [92,93]. Examples of these psychoactive drugs include analgesics, anticonvulsant, anesthetics,

Table 2: Neurotransmitter Systems in the Brain [33,45-53]

System	Pathway origin and projections	Regulated cognitive processes and behaviors
Noradrenaline system [45-47]	Noradrenergic pathways: □ Locus coeruleus (LC) projections - LC → Amygdala and Hippocampus LC → Brain stem and Spinal cord LC → Cerebellum LC → Cerebral cortex LC → Hypothalamus LC → Tectum LC → Thalamus LC → Ventral tegmental area □ Lateral tegmental field (LTF) projections - LTF → Brain stem and Spinal cord LTF → Olfactory bulb	Anxiety Hunger Arousal Circadian rhythm Cognitive control Working memory Reward perception Negative emotional memory Medullary control of respiration
Dopamine system [47-49]	Dopaminergic pathways: □ Ventral tegmental area (VTA) projections - VTA → Amygdala VTA → Cingulate cortex VTA → Hippocampus VTA → Nucleus accumbens (i.e. mesolimbic pathway) VTA → Olfactory bulb VTA → Prefrontal cortex (i.e. mesocortical pathway) □ Nigrostriatal projections - Substantia nigra → Caudate nucleus and putamen □ Tuberoinfundibular pathway - Arcuate nucleus → Median eminence	Mood Aversion Motivation Cognitive control Working memory Reward perception Motor system function Positive reinforcement Sexual arousal, orgasm, and refractory period
Histamine system [50]	Histaminergic pathways: □ Tuberomammillary nucleus (TMN) projections - TMN → Cerebral cortex TMN → Hippocampus TMN → Neostriatum TMN → Nucleus accumbens TMN → Amygdala TMN → Hypothalamus	Sleep Arousal Learning Memory Feeding and energy balance
Serotonin system [45, 47, 51, 52]	Serotonergic pathways: Caudal nuclei (CN): Raphe magnus, raphe pallidus, and raphe obscurus □ Caudal projections - CN → Cerebral cortex CN → Thalamus CN → Caudate-putamen and nucleus accumbens CN → Substantia nigra and ventral tegmental area Rostral nuclei (RN): Nucleus linearis, dorsal raphe, medial raphe and raphe pontis □ Rostral projections - RN → Amygdala RN → Cingulate cortex RN → Hippocampus RN → Hypothalamus RN → Neocortex RN → Septum RN → Thalamus RN → Ventral tegmental area	Sleep Arousal Appetite satiety Reward perception Sensory perception Body temperature regulation Emotion and mood, potentially including aggression

(Table 2). Continued.

System	Pathway origin and projections	Regulated cognitive processes and behaviors
Acetylcholine system [45, 47, 53]	Cholinergic pathways: Forebrain cholinergic nuclei (FCN): Nucleus basalis of Meynert (nbM), medial septal nucleus and diagonal band □ Forebrain nuclei projections - FCN → Hippocampus FCN → Cerebral cortex FCN → Limbic cortex and sensory cortex Brainstem cholinergic nuclei (BCN): Pedunculopontine nucleus, laterodorsal tegmentum, medial habenula and parabigeminal nucleus □ Brainstem nuclei projections - BCN → Ventral tegmental area BCN → Thalamus	Arousal Emotion Learning Reward perception Short-term memory Motor system function

Table 3: Neurotransmitter Imbalance and Associated Disorders [61-90]

Disorder	Pathophysiology
Alzheimer's disease (AD) [61-63]	Extracellular β-amyloid pledges, intracellular neurofibrillary tangles and senile plaques, predominantly in the limbic system (e.g. hippocampus), in the association area of the cortex and in neurons that synthesize and use acetylcholine (e.g., in the nbM and its wide projections to the cortex).
Anxiety [64-66]	Imbalance of endogenous inhibitors and stimulators of the GABA receptor may result in reduced activity of GABA. Additionally, these inhibitors and stimulators may also trigger imbalances in norepinephrine and 5-HT responses.
Autism [67-68]	Possible hyperserotonemia, which is accountable for 30 to 50% of autistic people, with no proof of central 5-HT abnormalities.
Brain injury [69, 70]	Neuronal death may take place due to the injuries (e.g. prolonged seizures, hypoxia, trauma) stimulating excessive secretion of excitatory neurotransmitters (e.g. glutamate) and buildup of intracellular calcium ion (Ca^{++}).
Depression [71, 72]	Critical aberrations in cholinergic, catecholaminergic (i.e. noradrenergic, dopaminergic) and 5-HT transmission possible association of other hormones and neuropeptides (e.g. substance P, dopamine, acetylcholine, GABA).
Seizure disorders [73, 74]	Increased activity of glutamate or reduced activity of GABA can cause seizures comprising of abrupt synchronous high-frequency firing by localized groups of neurons in certain brain areas.
Huntington's disease [75, 76]	Major neuronal injury in the cortex and striatum owing to polyglutamine expansion (i.e. encoded by CAG repeat), generated by an atypical gene on chromosome 4 (i.e. the anomalous gene overproduces the protein huntingtin, which may cartel with molecules that persuade extreme stimulation of cells by excitatory amino acid neurotransmitters such as glutamate).
Mania [77, 78]	Increased norepinephrine and dopamine action, abridged 5-HT levels and anomalous glutamate neurotransmission.
Neuroleptic malignant syndrome [79, 80]	Muscle rigidity, change in mental status fever and autonomic instability can take place due to the blockage of dopamine (D2) receptors by drugs (e.g. antipsychotic drugs, methylphenidate) or due to the sudden withdrawal of a dopaminergic agonist.
Pain [81, 82]	Tissue injury can trigger secretion of glutamate and substance P in the posterior horn of the spinal cord. Furthermore, this tissue injury can also cause release of other macromolecules including bradykinin, neurokinin A and calcitonin gene-related protein (i.e. located mainly in the lamina II and IV of the spinal cord) that mediate pain gestures. Further inflection of these gestures by endorphins (i.e. in the spinal cord) and by 5-HT and norepinephrine (i.e. in the descending pathways that originate in the brain).
Parkinsonism [83, 84]	Blockage of dopaminergic receptors by antipsychotic drugs can cause inhibition of the dopaminergic system.
PD [85, 86]	Alteration of the dopamine/acetylcholine balance and the subsequent striatal acetylcholine over activity are often to be involved with the loss of dopaminergic neurons of the pars compacta in the substantia nigra and other areas, with decreased levels of dopamine and metenkephalin.
Schizophrenia [87, 88]	Increased presynaptic discharge, synthesis of dopamine, sensitivity or density of postsynaptic D2 receptors, or a combination.
Tardive dyskinesia [89, 90]	Hypersensitive D2 receptors owing to prolonged blockade by antipsychotic drugs.

Table 4: Psychoactive Drugs and their Primary Neurotransmitter or Receptor and Mode of Action [101-120]

Neurotransmitter or Receptor	Mode of Action	Examples
Acetylcholine [101,102]	Acetylcholine receptor agonists (i.e. cholinergics)	Arecoline, nicotine, piracetam
	Acetylcholine receptor antagonists (i.e. muscarinic antagonists)	Scopolamine, benzatropine, dimenhydrinate, diphenhydramine, doxylamine, atropine, quetiapine, olanzapine, most tricyclics
	Acetylcholine receptor antagonists (i.e. nicotinic antagonists)	Memantine, bupropion
Adenosine [103]	Adenosine receptor antagonists	Caffeine, theobromine, theophylline
Dopamine [104]	Dopamine reuptake inhibitors	Cocaine, bupropion, methylphenidate, certain TAAR1 agonists like amphetamine, phenethylamine, and methamphetamine
	Dopamine releasers	Cavendish bananas, TAAR1 agonists like amphetamine, phenethylamine and methamphetamine
	D2 receptor agonists	Pramipexole, ropinirole, L-3,4-Dihydroxyphenylalanine, memantine
	D2 receptor antagonists	Haloperidol, droperidol, many antipsychotics (e.g. risperidone, olanzapine, quetiapine)
	D2 receptor partial agonists	Lysergic acid diethylamide (LSD), aripiprazole
GABA [105]	GABA reuptake inhibitors	Tiagabine, vigabatrin, deramciclane
	GABA receptor agonists	Ethanol, niacin, barbiturates, diazepam, clonazepam, lorazepam, temazepam, alprazolam and other benzodiazepines, zolpidem, eszopiclone, zaleplon and other nonbenzodiazepines, muscimol
	GABA receptor antagonists	Thujone, bicuculline
Norepinephrine [106]	Norepinephrine reuptake inhibitors	Most non-selective serotonin reuptake inhibitors (SSRIs) antidepressants such as amoxapine, atomoxetine, bupropion, venlafaxine, quetiapine, tricyclics, methylphenidate, serotonin and norepinephrine reuptake inhibitors (SNRIs) such as duloxetine, venlafaxine, cocaine, tramadol and certain TAAR1 agonists like amphetamine, phenethylamine, methamphetamine.
	Norepinephrine releasers	Ephedrine, pseudoephedrine, amphetamine, phenethylamine, methamphetamine
	Norepinephrine receptor agonists	Clonidine, guanfacine, phenylephrine
	Norepinephrine receptor antagonists	Carvedilol, metoprolol, mianserin, prazosin, propranolol, trazodone, yohimbine, olanzapine
Serotonin [107]	Selective 5-HT receptor agonists	Methylphenidate, LSD, psilocybin, mescaline
	5-HT reuptake inhibitors	Most antidepressants including tricyclics such as imipramine, SSRIs such as fluoxetine, sertraline and citalopram, and SNRIs such as duloxetine and venlafaxine, cocaine, tramadol, and certain TAAR1 agonists like amphetamine, tryptamine, and methamphetamine
	5-HT releasers	Fenfluramine, 3,4-Methylenedioxymethamphetamine (MDMA), tryptamine
	5-HT receptor antagonists	Ritanserin, mirtazapine, mianserin, trazodone, cyproheptadine, memantine, atypical antipsychotics (e.g. risperidone, olanzapine, quetiapine)
α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor [108]	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor positive allosteric modulators	Aniracetam, piracetam
	AMPA receptor antagonists	Kynurenic acid, topiramate
Cannabinoid receptor [109]	Cannabinoid receptor partial agonists	Anandamide, cannabidiol, cannabinol
	Cannabinoid receptor inverse agonists	Rimonabant

(Table 4). Continued.

Neurotransmitter or Receptor	Mode of Action	Examples
Fatty acid amide hydrolase inhibitors [110]	Methoxy arachidonyl fluorophosphonate, N-arachidonylglycine	–
Melanocortin receptor [111]	Melanocortin receptor agonists	Bremelanotide
NMDA receptor [112]	NMDA receptor antagonists	Ethanol, ketamine, Nitrous oxide, glutamate, memantine (used for moderate to severe AD)
γ-hydroxybutyrate (GHB) receptor [113]	GHB receptor agonists	GHB, amisulpride, *trans*-4-hydroxycrotonic acid
Sigma receptor [114]	Sigma-1 receptor agonists	Cocaine, fluvoxamine, ibogaine, opipramol
Opioid receptor [115]	μ-opioid receptor agonists	Morphine, heroin, oxycodone, codeine
	μ-opioid receptor partial agonists	Buprenorphine
	μ-opioid receptor inverse agonists	Naloxone
	μ-opioid receptor antagonists	Naltrexone
	κ-opioid receptor agonists	Butorphanol, nalbuphine, pentazocine, ibogaine
	κ-opioid receptor antagonists	Buprenorphine
Histamine receptor [116]	H_1 histamine receptor antagonists	Diphenhydramine, doxylamine, mirtazapine, mianserin, quetiapine, olanzapine, meclozine, dimenhydrinate, most tricyclics
Monoamine oxidase [117]	Monoamine oxidase inhibitors	Phenelzine, iproniazid, tranylcypromine, selegiline, rasagiline, moclobemide, isocarboxazid, linezolid, benmoxin
Melatonin receptor [118]	Melatonin receptor agonists	Ramelteon
Imidazoline receptor [119]	Imidazoline receptor agonists	Apraclonidine, clonidine, moxonidine, rilmenidine
Orexin receptor [120]	Orexin receptor agonists	Modafinil

hormonal preparations and antiparkinson medication or drugs such as anxiolytic and hypnotic drugs which are used to treat neuropsychiatric disorders. Certain psychoactive substances are also used in the detoxification purposes and in the rehabilitation programs for psychotropic drug users [94].

Neurochemistry of Psychoactive Drugs

Alterations in a person's cognition, perception, mood and behavior can be temporarily triggered by psychoactive drugs [95]. In many ways psychoactive drugs can stimulate these changes by affecting the brain. In the brain, these drugs particularly act on one or more neurotransmitter or on neuroreceptor and the drugs which increase the activity of these systems are known as agonists. In case of neurotransmitters, these agents increase their synthesis and also by reducing their reuptake from the synapses and by simulating the action by directly binding to the postsynaptic receptors [96]. In contrast, drugs that decrease the activity of the neurotransmitters are called as antagonists and they act by altering the synthesis or by blocking postsynaptic receptors, as a result binding of the neurotransmitters will be inhibited [97].

Structure and functions of the neurons can also be changed due to the exposure to a psychoactive substance. These structural and functional changes are generated by the nervous system to re-establish the homeostasis which is disrupted by the presence of these psychoactive drugs. Exposure to an antagonist for a certain neurotransmitter can upsurge the number of receptors for that particular neurotransmitter. Furthermore the receptors themselves may also

become more responsive to neurotransmitters; this phenomenon is known as sensitization [98]. On the contrary, there is also a process known as desensitization or tolerance, which involves overstimulation of certain receptors for a specific neurotransmitter or reduction in numbers these receptors and their sensitivity. Although sensitization and desensitization processes are likely to place with chronic exposure, they may also take place just after a single exposure. These processes are believed to take part in drug dependence and addiction [99]. Physical dependence on antidepressants or anxiolytics may lead to anxiety or worsen depression and these are most common withdrawal symptoms of these agents.

It should be noted that many drugs act on more than one transmitter or receptor in the brain [100]. In the Table **4** a brief of notable drugs and their main neurotransmitter or receptor and method of action is presented.

NEUROPEPTIDES

Neuropeptides are small protein-like molecules that are synthesized in the cell body and for neuronal communication [121]. These are involved with various brain functions, including learning and memory, analgesia, food intake, social behaviors, metabolism and reproduction [122, 123]. The basic differences between neuropeptide and peptide hormone are the cell types that secrete and respond to the molecule. Neuropeptides are primarily secreted from neuronal cells and signal to neighboring neurons. Whereas, neuroendocrine cells mainly secrete peptide hormones and following secretion they travel via the blood to distant target tissues to induce a response [124]. Prohormone convertases and carboxypeptidases are same set of enzymes that synthesize both neuropeptides and peptide hormones. These enzymes selectively cut the peptide precursor at particular processing sites to produce the bioactive peptides

Table 5: Bioactive Peptides and their Alliance [34]

Bioactive Peptide	Group
Substance P, substance K (tachykinins)	Brain and gastrointestinal peptides
Neurotensin	
Cholecystokinin	
Gastrin	
Bombesin	
Galanin	Neuronal
Neuromedin K	
Neuropeptidey	
Peptide YY	
Cortikotropin releasing hormone	Hypothalamic releasing factors
Growth hormone releasing hormone	
Gonadotropin releasing hormone	
Somatostatin	
Thyrotropin releasing hormone	
Adrenocorticotropic hormone	Pituitary hormones
Growth hormone	
Prolactin	
Lutenizing hormone	
Thyrotropin	
Oxytocin	Neurohypophyseal peptides
Vasopressin	
Atrial natriuretic peptide	Neuronal and endocrine
Vasoactive intestinal peptide	
Enkephalines (met-, leu-)	Opiate peptides

[125]. The associations of the bioactive peptides are presented in Table **5**.

Neurochemistry of Neuropeptides

Neuropeptides control communications of neurons by acting on cell surface receptors and these neuropeptides sometimes co-released with various small-molecule neurotransmitters [126]. Precursors of neuropeptides are encoded by the human genome that comprises about 90 genes. Currently, in the mammalian brain, 100 different peptides are found to be released by different populations of neurons [127]. Peptides, neurotransmitters and gasotransmitters are the common signals that neurons use in different neuronal communication. Unlike various conventional neurotransmitters, once secreted peptides are not recycled back into the cell and they are distinctive amongst these cell to cell signaling molecules in several ways [128]. Additional difference is that after release, peptides are changed by extracellular peptidases. Sometimes these extracellular cleavages deactivate the biological activity. Instead in some cases, the extracellular cleavages upsurge the affinity of a peptide for a particular receptor while reducing its affinity for another receptor [129]. A list of neuroactive peptides coexisting with other neurotransmitters is given in Table **6**.

Many populations of neurons have distinctive biochemical phenotypes [130]. For example, in one subpopulation of about 3000 neurons in the arcuate nucleus of the hypothalamus, three anorectic peptides are co-expressed: α-melanocyte-stimulating hormone (α-MSH), galanin-like peptide and cocaine-and-amphetamine-regulated transcript (CART) and in another subpopulation two orexigenic peptides are co-expressed, neuropeptide Y and agouti-related peptide (AGRP) [129]. It has been found that different populations of neurons contain distinct biochemical phenotypes [130]. For example, in one subpopulation of about 3000 neurons in the arcuate nucleus of the hypothalamus, 3 anorectic peptides are co-expressed: galanin-like peptide, α-melanocyte-stimulating hormone and CART and in another subpopulation 2 orexigenic peptides are co-expressed such as AGRP and neuropeptide Y [129]. However, in addition to these peptides in the arcuate nucleus, dynorphin, galanin, β-endorphin, ghrelin, encephalin, neurotensin, somatostatin, growth-hormone releasing hormone and neuromedin U are also found to be expressed in subpopulations of arcuate neurons [131]. All of these peptides are secreted centrally and act on other neurons at specific receptors. The neuropeptide Y neurons likewise make the conventional inhibitory neurotransmitter GABA.

Information processing mediated by peptide signals is different from conventional neurotransmitters and many of them act in different ways for example, as stated earlier oxytocin and vasopressin have prominent and explicit effects on social behavior's including maternal behavior and bonding with the child [132, 133].

Table 6: Neuroactive Peptides and its Coexistent with other Neurotransmitters [129]

Neuroactive Peptides	Coexisting Neurotransmitters
Norepinephrine	Galanin Enkephalin Neuropeptide Y
GABA	Somatostatin Cholecystokinin Neuropeptide Y
Acetylcholine	Vasoactive intestinal peptide Substance P
Dopamine	Cholecystokinin Neurotensin Glucagon-like peptide-1
Epinephrine	Neuropeptide Y Neurotensin
5-HT	Substance P Thyrotropin-releasing hormone Enkephalin

CONCLUSION

The brain is outfitted with diversity of molecules that enable neurons to communicate with each other. The fact that one can read this text, remember what has been read and even breathe during the entire time that these events take place relies on the amazing chemistry that occurs in the brain and the nerve cells with which it communicates. Life in the human body is tortuous. Everything is necessary for our survival that makes us feel happy. Our brain has self-produced neurochemicals that turn the pursuits and struggles of life into pleasure and make us feel happy when we achieve them. Apt neuronal communication is obligatory for typical existent.

ABBREVIATIONS

5-HT = Serotonin

D2 = Dopamine

GABA = γ-aminobutyric acid

TAAR1 = Trace amine-associated receptor 1

LC = Locus coeruleus

LTF = Lateral tegmental field

VTA = Ventral tegmental area

TMN = Tuberomammillary nucleus

CN = Caudal nuclei

RN = Rostral nuclei

FCN = Forebrain cholinergic nuclei

BCN = Brainstem cholinergic nuclei

nbM = Nucleus basalis of Meynert

PD = Parkinson's disease

AD = Alzheimer’s disease

LSD = Lysergic acid diethylamide

SSRI = Selective serotonin reuptake inhibitor

SNRIs = Serotonin and norepinephrine reuptake inhibitors

MDMA = 3,4-Methylenedioxymethamphetamine

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

GHB = γ-hydroxybutyrate

CART = Cocaine-and-amphetamine-regulated transcript

AGRP = Agouti-related peptide

AUTHORS’ CONTRIBUTIONS

This work was carried out in collaboration between all authors. Author MSU designed the study, wrote the protocol, managed the analyses of the study and prepared the draft of the manuscript. Authors MSU, AAM, MTK, MN, FW, MMB, MSR and MTI managed the literature searches and participated in manuscript preparation. Authors ZKL, MMAD and MSA reviewed the scientific contents of the manuscript. All the authors read and approved the final manuscript.

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COMPETING INTERESTS

The authors proclaim that they have no competing interests.

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