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 neural network of evolution. 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. Neurons 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
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 tranquillizers 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].
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  | Noradrenergic pathways: □ Locus coeruleus (LC) projections - LC → Amygdala and Hippocampus   | Anxiety, Hunger, Arousal, Circadian rhythm, Cognitive control, Working memory, Reward perception, Negative emotional memory, Medullary control of respiration |
|                       | 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                                                                                 |                                                                                                           |
| Dopamine system       | Dopaminergic pathways: □ Ventral tegmental area (VTA) projections - VTA → Amygdala                  | Mood, Aversion, Motivation, Cognitive control, Working memory, Reward perception, Motor system function, Positive reinforcement, Sexual arousal, orgasm, and refractory period |
|                       | VTA → Cingulate cortex                                                                               |                                                                                                           |
|                       | VTA → Hippocampus                                                                                    |                                                                                                           |
|                       | VTA → Nucleus accumbens (i.e. mesolimbic pathway) VTA → Olfactory bulb                               |                                                                                                           |
|                       | VTA → Prefrontal cortex (i.e. mesocortical pathway) VTA → Nigrostriatal projections - Substantia nigra → Caudate nucleus and putamen |                                                                                                           |
|                       | □ Tuberoinfundibular pathway - Arcuate nucleus → Median eminence                                      |                                                                                                           |
| Histamine system      | Histaminergic pathways: □ Tuberomammillary nucleus (TMN) projections - TMN → Cerebral cortex        | Sleep, Arousal, Learning, Memory, Feeding and energy balance                                               |
|                       | TMN → Hippocampus                                                                                    |                                                                                                           |
|                       | TMN → Neostriatum                                                                                    |                                                                                                           |
|                       | TMN → Nucleus accumbens                                                                              |                                                                                                           |
|                       | TMN → Amygdala                                                                                       |                                                                                                           |
|                       | TMN → Hypothalamus                                                                                   |                                                                                                           |
| Serotonin system      | Serotonergic pathways: □ Caudal nuclei (CN): Raphe magnus, raphe pallidus, and raphe obscurus       | Sleep, Arousal, Appetite satiety, Reward perception, Sensory perception, Body temperature regulation, Emotion and mood, potentially including aggression |
|                       | □ 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                                                                          |                                                                                                           |
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

Regulated cognitive processes and behaviors

- 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 coat 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, neuropeptide 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. |
| 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, phenylethylamine, and methamphetamine |
|                             | Dopamine releasers | Cavendish bananas, TAAR1 agonists like amphetamine, phenylethylamine 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, bicculline |
| 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, phenylethylamine, methamphetamine. |
|                             | Norepinephrine releasers | Ephedrine, pseudoephedrine, amphetamine, phenylethylamine, 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 | Ritalaner, mirfazapine, mianserin, trazodone, cyproheptadine, memantine, atypical antipsychotics (e.g. risperidone, olanzapine, quetiapine) |
| α-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid (AMPA) receptor [108] | α-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid (AMPA) receptor positive allosteric modulators | Aniracetam, piracetam |
|                             | AMPA receptor antagonists | Kynurenic acid, topiramate |
| Cannabinoid receptor [109]  | Cannabinoid receptor partial agonists | Anandamide, cannabidiol, cannabinoil |
|                             | 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] | H1 histamine receptor antagonists | Diphenhydramine, doxylamine, mirtazapine, mianserin, quetiapine, olanzapine, meclozine, dimenhydrinate, most tricyclics |
| Monoamine oxidase [117] | Monoamine oxidase inhibitors | Phentolamine, iproniazid, tranylcypromine, selegiline, rasagiline, moclobemide, isocarboxazid, linezolid, benoxapine |
| 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.

### 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                                       |                                 |
| Corticotropin releasing hormone                  | Hypothalamic releasing factors   |
| Growth hormone releasing hormone                 |                                 |
| Gonadotropin releasing hormone                   |                                 |
| Somatostatin                                     |                                 |
| Thyrotropin releasing hormone                    |                                 |
| Adrenocorticotropic hormone                      | Pituitary hormones              |
| Growth hormone                                   |                                 |
| Prolactin                                        |                                 |
| Luteinizing hormone                              |                                 |
| Thyrotropin                                      |                                 |
| Oxytocin                                         | Neurohypophyseal peptides       |
| Vasopressin                                      |                                 |
| Atrial natriuretic peptide                       | Neuronal and endocrine          |
| Vasoactive intestinal peptide                    |                                 |
| Enkephalines (met-, leu-)                        | Opiate peptides                 |
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, neotensin, 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              |
|                      | Neotensin                    |
|                      | Glucagon-like peptide-1      |
| Epinephrine          | Neuropeptide Y               |
|                      | Neotensin                    |
| 5-HT                 | Sub stance P                 |
|                      | Thrytropin-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  
bM = 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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