Neurotransmitters

Vikas Dhikav

Clinical Case Example

- A 61-year-old male complains of intermittent weakness in legs and muscle fatigue, progressively worsening over the past month. The patient used to jog in the nearby park until a few years back, but now he has difficulty doing the same. His symptoms of profound leg weakness and fatigue are attributed to age by local doctors and his underlying history of heart disease. Over the past few months, he also reports having noted “eye strain” while reading newspaper. He has developed intermittent double vision that seems to be worse when reading at bed at night.

Answer: Patient has a diagnosis of myasthenia gravis and needs treatment with anticholinesterases like pyridostigmine. The drug is started in 5 to 10 mg three to four times daily. The drug acts by boosting the activity of peripheral neurotransmitter at the neuromuscular junction (NMJ) (acetylcholine [ACh]).

Introduction

Neurotransmitter is a substance released from the axon terminal of a neuron which binds to the receptor and produces physiological response. In the early years of the 20th century, the neural basis of neurotransmission was discovered. During this period, the functions of acetylcholine (ACh) and adrenaline were realized, the oldest known neurotransmitters. Fig. 3.1 shows a general introduction to the process of neurotransmission. Details of the process are shown in Fig. 3.2. Metabolic mechanisms of handling neurotransmitters are illustrated in Fig. 3.3.

As per conventional wisdom, neurotransmitters are synthesized in the neuron and become localized in the presynaptic terminal after synthesis. They bind to the receptor site on the postsynaptic membrane and are removed from its specific site of action by a specific mechanism. Glutamate and aspartate are abundant neurotransmitters found in cerebral cortex, spinal cord (aspartate), striatum, dentate gyrus (hippocampus), cerebellum, and spinal cord. The neurotransmitter has excitatory influences on basal nuclei.

Glycine is the major inhibitory neurotransmitter of the brain and spinal cord, which is found in interneurons of spinal cord (Renshaw cells) and neurons of subthalamic nuclei projecting to globus pallidus.

Neurotransmitters exhibit their pharmacological effects by acting on the receptors. Receptors are genetically coded proteins embedded in cell membrane, which mediate...
Neurotransmitters released into the synapse cleft do not remain there and are subject to either inactivation or reuptake by presynaptic neurons. Reuptake refers to when the presynaptic neuron takes up most of the neurotransmitter molecules intact and reuses it again for synaptic action. Transporters present presynaptically are special membrane proteins that facilitate reuptake process. For example, serotonin is taken back up into the presynaptic terminals and is stored for future action. Commonly used antidepressants like selective serotonin reuptake inhibitors (SSRIs) block the reuptake process.

It was Sherrington who proposed that cells in the nervous system “talk” to each other, using a group of chemicals (now known as neurotransmitters). He also suggested that there is a gap between cells, and this is known as synapse. The neurotransmitters flow across the synapse and produce the responses.

Precursors, for example, levodopa and noradrenaline, are raw materials that eventually get converted into dopamine and adrenaline, respectively. Making of neurotransmitters is known as biosynthesis, and these are stored in
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Inactivation and reuptake in presynaptic neurons are the two major events that take place at the synapse. For example, acetylcholine (ACh) is broken down by acetylcholinesterase (AChE) into acetate and choline which are recycled. Serotonin and catecholamine molecules are converted into inactive chemicals. Catechol-o-methyltransferase (COMT) and monoamine oxidase (MAO) are enzymes that convert catecholamine transmitters into inactive chemicals that are eliminated in urine. The major physiologically important fate of a neurotransmitter is postsynaptic action.

**Box 3.1: Categories of neurotransmitters**

- **Ester**: ◊ ACh.
- **Biogenic amines**: ◊ Catecholamines: □ Dopamine, norepinephrine, and epinephrine. ◊ Indolamines: □ Serotonin (5-hydroxytryptamine [5-HT]). □ Histamine.
- **Neuropeptides**: ◊ Substance P. ◊ Endorphins and enkephalins. ◊ Somatostatin, gastrin, cholecystokinin, oxytocin, vasopressin.
- **Purines**: ◊ Adenosine. ◊ Adenosine triphosphate (ATP).
- **Small molecules, e.g., gases and lipids**: ◊ Nitric oxide. ◊ Carbon monoxide. ◊ Cannabinoids.

vesicles (Golgi bodies). The neurotransmitter, once synthesized, will be transported via neurofilaments and microtubules. Docking of calcium involves influx, leading to vesicle movement and eventual exocytosis. Neurotransmitter reaches into synaptic gap and produces pharmacological action by binding to postsynaptic receptors. Reuptake into presynaptic neurons helps recover the neurotransmitter (Cognitive Neurosciences Society, 2019). **Box 3.1** lists several neurotransmitters found in the brain.

**Receptor Types**

**Ionotropic**

Ionotropic receptors work very fast and play an important role in fast neurotransmission. Each ionotropic receptor is made of several subunits, which together form the complete receptor, for example, GABA<sub>A</sub> receptors have a pentameric structure. At the center of the receptor is a channel or pore to allow flow of neurotransmitter, leading to generation of physiological effects. At rest, receptor channels are closed, and when neurotransmitter binds to the channel, it immediately opens. When ligand leaves binding site, channel quickly closes.

**Metabotropic**

Metabotropic receptors work more slowly than ionotropic receptors as their pharmacological effects involve a series of steps to produce combined effects. Although it takes longer for postsynaptic cell to respond, response is
somewhat longer-lasting compared to ionotropic receptors. These receptors comprise a single protein subunit, winding back-and-forth through cell membrane seven times (transmembrane domains). They do not possess a channel or pore like ionotropic receptors. Rather, they span the cell membrane like snakes; hence, they are known as serpentine receptors.10

Details of both these and other receptor types are described in the chapter on pharmacodynamics.

It is important to differentiate between a few terms here. Neurotransmitters are chemicals synthesized within the axon, travel short distances, and are fast acting.

Neuromodulators, on the other hand, are also synthesized within the cell body of neurons, travel farther distances via diffusion, but are slower acting. Neurohormones are synthesized in endocrine glands, also travel to far distances, and produce pharmacological effects by binding to receptors on the cell or nuclear membrane.

**Early Years**

In the beginning, it was believed that only ACh and adrenaline were present inside the brain. Later, it was realized that the brain also contains dopamine, serotonin, and several other neurotransmitters. Gaddum and his colleagues showed that 5-HT (also called serotonin) was present in the brain and had neurotransmitter properties. Lysergic acid dimethyl was found to be hallucinogenic during the early 1950s, and this was the period which witnessed the advent of several psychopharmacotherapeutic agents.

**Neurochemical Basis of Neurotransmission**

After a presynaptic neuron is stimulated, the delay is very short (e.g., 0.3 ms) for the postsynaptic neuron to respond. This is too long for electric transmission, which is lightning fast. If we stimulate the postsynaptic neuron, no response in the presynaptic one occurs. Polarization of communication between neurons occurs only when presynaptic neuron stimulates the postsynaptic neuron. Stimulation of presynaptic neuron may result in postsynaptic inhibition, too, in some neuronal circuits. All the events described here are difficult to explain in terms of direct passage of electrical currents between neurons. All this happens in a series of complicated steps (Fig. 3.1). However, to be able to call a putative chemical as a neurotransmitter, properties.

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**Table 3.1** Major classes of neurotransmitters

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Receptors</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoamines (dopamine, norepinephrine, serotonin)</td>
<td>GPCRs</td>
<td>Slow changes in excitability</td>
</tr>
<tr>
<td>ACh</td>
<td>GPCRs</td>
<td>Slow changes in excitability</td>
</tr>
<tr>
<td>Amino acids (GABA, glycine)</td>
<td>Ion channels</td>
<td>Rapid inhibition</td>
</tr>
<tr>
<td>Glutamate (excitatory)</td>
<td>Ion channels</td>
<td>Rapid excitation</td>
</tr>
</tbody>
</table>

Abbreviations: ACh, acetylcholine; GABA, gamma-aminobutyric acid; GPCRs, G-protein-coupled receptors.
certain criteria are needed (Box 3.2). Major classes of neurotransmitters are given in Table 3.1.

**What Is a Neurotransmitter?**

This is a chemical substance synthesized, stored, and released by a neuron. However, there are several criteria that need to be fulfilled before a chemical can be called a neurotransmitter. However, these are general guidelines rather than rigid rules as enlisted in Box 3.2.

- Following depolarization, the substance is released in the synaptic cleft.
- There are specific receptors for the neurotransmitter present in the synaptic cleft.
- If the chemical substance is applied by artificial method, say using ionotophoresis, then the result produced should be same as that of natural stimulation.
- Specific antagonists available must be able to block the effect produced by the neurotransmitter.
- A specific mechanism for terminating the action of putative neurotransmitter should be there.
- Specific receptors could be found for some of the receptors in the presynaptic location. These, when stimulated, inhibit the release of neurotransmitter. These are known as “autoreceptors.”

Several drugs act on the neurotransmitter systems, and they are used to treat psychiatric and neurological illnesses (Fig. 3.4). The entire process of release of a neurotransmitter from presynaptic neuron is explained in Fig. 3.5.

**Types of Neurotransmitters**

Neurotransmitters capable of binding to the receptor on the brain neuron surfaces are of several types:

- Amino acids: This is a class of neurotransmitters that are organic molecules containing an amino group ($\text{NH}_2$).
- Peptides: Peptides contain a chain of two or more amino acids, smaller than proteins.
- Proteins: These are long chains of amino acids which contain carbon, hydrogen, oxygen, nitrogen, and, usually, sulfur.
Synapse

Otto Loewi, Dale, and Sherrington worked exhaustively to propagate this concept of synapse and chemical neurotransmission across decades. Synapse is a “gap” between the axon of one nerve and the dendrite of the next one. The average neuron has 1,000 synapses with other neurons. Dendrites receive incoming information from other neurons. Synapses make up most of the surface area of the neuron and the branches of neurons (dendritic), and their spines can number in the thousands.

Mechanism of Action of Neurotransmitters

Broadly, neurotransmitters could have stimulatory or inhibitory effects. Some of the receptors such as GABA are linked to several metabolic steps and hence produce slow effects. Others such as nicotinic receptors are linked to sodium channels. This allows a large amount of sodium ions to enter the cells and hence produce rapid effects.

There are dozens of different neurotransmitters in the neurons. Each neuron generally synthesizes and releases a single type of neurotransmitter (Table 3.2).

Acetylcholine

ACh is present in both central nervous system (CNS) and peripheral nervous system (PNS) (Fig. 3.6). It is the first neurotransmitter described and is the most abundant of them all. Apart from the brain, it is released at the NMJ and autonomic synapses. It is synthesized and broken down by the enzyme acetylcholinesterase (Fig. 3.5).

Fig. 3.5 Process of neurotransmitter release. Impulses from action potential generated in cell body open ion channels for Ca²⁺ ions, and this increases Ca²⁺ concentration in the axon terminal which, in turn, initiates the release of the neurotransmitter. Neurotransmitter released from its vesicle after crossing the “gap” or synaptic cleft attaches to a protein receptor on the dendrite. Interaction of neurotransmitter with receptors open postsynaptic membrane ion channel for Na⁺. After the action is over, the neurotransmitter is either degraded by an enzyme or taken back into the presynaptic membrane by a transporter or reuptake pump.

Table 3.2 Major neurotransmitters and their roles

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>Controls muscle tone, movements, and memory</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Mediates pleasure and reward system in the brain. It also has inhibitory control</td>
</tr>
<tr>
<td>GABA</td>
<td>Major inhibitory neurotransmitter in the brain</td>
</tr>
<tr>
<td>Glycine</td>
<td>Major inhibitory neurotransmitter in the spinal cord</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Acts both as a neurotransmitter and hormone. Mediates flight and flight response</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Mediates mood, motivation, has some role in memory and pain pathways</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Most abundant excitatory neurotransmitter in the brain</td>
</tr>
</tbody>
</table>
Neurotransmitters

Acetylcholine

Fig. 3.6 Acetylcholine (ACh) is a quaternary amine synthesized locally in the brain. Peripherally synthesized ACh does not enter the blood–brain barrier (BBB); hence, all functions ascribed to it are the functions of local ACh. Several drugs like donepezil can boost the function of ACh in the brain.

as a combination of acetyl-coenzyme A (CoA) and choline; the former comes from Krebs cycle in the mitochondria, and the latter is present in the food (eggs, legumes). In the PNS, it is not only responsible for controlling muscle tone but also a major neurotransmitter at NMJ. ACh is synthesized by enzyme choline acetyltransferase and is degraded by the enzyme acetylcholinesterase (AChE). Major drugs/chemicals acting on this system are listed in Box 3.3.

ACh is the most abundant neurotransmitter of excitatory type, with a widespread distribution throughout the brain. ACh, present in several areas, perform vital functions with clinical implications (Box 3.4). Also, ACh is an attractive therapeutic target in certain disorders like Alzheimer’s disease. Inhibition of degradation of ACh is useful in treating this disorder. ACh receptors are described in Fig. 3.7.

Clinical Aspects

Cholinergic system undergoes degeneration in Alzheimer’s disease, the leading cause of dementia. The degeneration occurs in ACh stores of the brain, for example, nucleus basalis of Meynert.9

Box 3.3: Major drugs/chemicals acting on ACh

- **Black widow spider venom:**
  - ◇ Increases release of ACh.
- **Botulinum toxin:**
  - ◇ Blocks release of ACh.
- **Curare:**
  - ◇ Blocks nicotinic receptors.
- **Insecticides:**
  - ◇ AChE inhibitors (atropine is an antidote).

Box 3.4: Major areas of ACh and its roles

- Dorsolateral pons—rapid eye movement sleep.
- Basal forebrain—perceptual learning.
- Medial septum—formation of memories.
- Basal ganglia—extrapyramidal motor responses.
- Vestibular nucleus—motion sickness.

Fig. 3.7 Acetylcholine (ACh) receptors, like many other ligand-activated neurotransmitter receptors, consist of two major subtypes: metabotropic muscarinic receptors and the ionotropic nicotinic receptors. The nicotinic receptors are ligand-gated receptors that allow passage to Na+ ions.

Monoamines

Monoamine neurotransmitters include dopamine, norepinephrine, epinephrine, and serotonin. These are also called as catecholamines due to the presence of catecholamine nucleus.3
These are released both in CNS and PNS and have wide-ranging roles in mood, arousal, emotion, and cognition. The most prominent of their roles in neuropsychopharmacology pertains to mood. Dopamine is important for mood, motivation, memory, and movements (4Ms), and serotonin too has important roles in mood, emotions, and memory. Epinephrine and norepinephrine have roles in arousal and attention. The pathways for synthesis of dopamine and serotonin are given in **Flowcharts 3.1 and 3.2**.

### Individual Catecholamines

Dopamine, norepinephrine, epinephrine, and serotonin are catecholamines. Cell bodies producing these are found primarily in the brainstem and branch profusely; hence, they produce widespread areas of physiological effect. They are important in neuropsychopharmacology as biogenic amine theory of depression is based upon monoamines and so is dopaminergic theory of schizophrenia. Dopaminergic system has an involvement in Parkinson’s disease. Several features make monoaminergic system special (**Box 3.5**) in brain functioning. Their location in the brain is given in **Table 3.3**.

### Dopamine

Dopamine is concentrated in neurons of the ventral tegmental area (VTA) and in the substantia nigra of the basal ganglia. Dopamine is

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**Box 3.5: Characteristics and functions of monoaminergic system**

- **Characteristics:**
  - Diffuse.
  - Fine, unmyelinated axons.
  - Metabotropic synapses.

- **Functions:**
  - Sleep.
  - Arousal.
  - Mood.
  - Hunger.

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**Flowchart 3.1** Catecholamine biosynthesis. Tyrosine, a small amino acid, is transported in the neurons of brain or adrenal medulla where the synthesis takes place. Tyrosine hydroxylase, the key enzyme of biosynthesis, converts phenylalanine into dihydroxyphenylalanine (DOPA). The enzyme DOPA decarboxylase then converts DOPA to dopamine. The enzyme dopamine β-hydroxylase then converts dopamine to norepinephrine. The last step of catecholamine biosynthesis is the conversion of norepinephrine to epinephrine, which involves a methylation reaction, in the presence of phenylethanolamine N-methyltransferase (PMNT).

**Flowchart 3.2** Serotonin biosynthesis. Serotonin, also known as 5-HT, is a monoamine neurotransmitter. It is derived from tryptophan and is found in the gastrointestinal tract, blood platelets, and CNS.
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Mesocortical pathway

Nigrostriatal pathway

Tuberoinfundibular pathway

Fig. 3.8 Various dopaminergic tracts in the brain. There are four major dopaminergic pathways, for example, mesolimbic pathway (generates positive symptoms of schizophrenia), mesocortical pathway (produces negative symptoms) when it undergoes hypofunctioning, nigrostriatal pathway (produces side effects like extrapyramidal symptoms and tardive dyskinesia), and tuberoinfundibular pathway, blockade of which can cause hyperprolactinemia.

Main dopaminergic systems are as follows:

- Nigrostriatal: The cell bodies located in substantia nigra and project to caudate nucleus and putamen. Blockade of this system leads to extrapyramidal symptoms.
- Mesolimbic system: It is commonly known as the reward system. The cell bodies are located in the VTA and project to nucleus accumbens (prefrontal subcortex), amygdala, and hippocampus. Emotional symptoms of schizophrenia are thought to be generated here.
- Mesocortical system: Mesocortical system is needed for short-term memory, planning, and strategy preparation. The cell bodies are located in the VTA and project to prefrontal cortex.

Norepinephrine

Norepinephrine was first discovered in the sympathetic branch of the autonomic nervous system. Cell groups containing norepinephrine are found in the locus coeruleus (LC), which projects all over the brain and partakes in the sleep–wake cycle, attention, and vigilance.

Norepinephrine is synthesized from dopamine. The cell bodies of most norepinephrine neurons are located in the regions of pons, medulla, and thalamus. Norepinephrine receptors could be excitatory or inhibitory. LC in the pons is rich in norepinephrine projections. The activation of

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Nucleus/cell body</th>
<th>Terminals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>Locus coeruleus, lateral tegmental area</td>
<td>Widespread effects in cerebral cortex, spinal cord, basal forebrain, thalamus, hypothalamus, brainstem, spinal cord</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Medulla</td>
<td>Thalamus, brainstem, spinal cord</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Substantia nigra, ventral tegmental area, arcuate nucleus</td>
<td>Basal ganglia, limbic system, cerebral cortex, cerebellum</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Raphe nucleus</td>
<td>Widespread projections in cerebral cortex, cerebellum, brainstem, spinal cord</td>
</tr>
</tbody>
</table>
neurons in this area leads to increased vigilance. Arousal response leads to sexual behavior. Details of adrenergic projections are given in Fig. 3.9.

**Epinephrine**

Sympathoexcitatory by nature, it is found in the adrenal medulla and in cell groups of the medulla (oblongata). It produces excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs), depending on the postsynaptic receptor. Its effects are implicated in movement, attention, learning, and addiction.

**Serotonin**

Serotonin is also known as 5-HT. The cell bodies are found in raphe nucleus, pons, and medulla (part of the reticular formation). The projections are mainly to the cerebral cortex, hippocampus, and basal ganglia. Serotonin has roles in many behaviors such as mood, control of eating, sleep, arousal, and pain pathways. It also plays important roles in the higher cognition and emotions. Fig. 3.10 describes various receptors related to serotonin.

Serotonin is extensively distributed in the brain. It is derived from the amino acid

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**Fig. 3.9** Diffuse adrenergic projections in the brain. The noradrenergic neurons, when activated, exerts diffuse effects on large areas of the brain. The effects are alertness and arousal. Anatomically, the noradrenergic neurons originate both in the locus coeruleus (LC) and the lateral tegmental field. The axons of the neurons in the LC act on adrenergic receptors present in the amygdala, cingulate gyrus, cingulum, hippocampus, hypothalamus, neocortex, striatum, and thalamus. On the other hand, axons of neurons of the lateral tegmental field act on adrenergic receptors in hypothalamus.

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**Fig. 3.10** Serotonin is one of the neurotransmitters with maximum number of receptors. At least 15 types and subtypes are known in this case, and they have multiple transduction mechanisms as well. Serotonin receptors have defined roles, for example, 5-HT1A has role in anxiety/depression (buspirone stimulates it), 5-HT1D has a role in migraine (sumatriptan stimulates it), 5-HT2 has roles in various central nervous system (CNS) behaviors and in cardiovascular system (CVS) (blocked by atypical antipsychotics), and 5-HT3 has roles in nausea and vomiting, especially due to chemotherapy and radiotherapy (blocked by ondansetron).
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Tryptophan. Depletion of serotonin in the brain leads to depression (monoamine theory of depression).

Serotonin was first identified as an element found in the blood which aided its clotting and produced vasoconstriction (serum tonic). 5-HT neurons are found mostly in the raphe nuclei that are located in the brainstem and that innervate all major brain areas. It is manipulated by antipsychotic drugs.

**Amino Acids**

Some amino acids that work as neurotransmitters do not need to be converted into active moieties to have action on synapses. Examples include glutamate (excitatory), GABA, and glycine (inhibitory). They play a major role in synaptic communication and are very effective over short distances due to their rapid action.

**Gamma-Aminobutyric Acid Receptors**

This is a pentameric structure with two major GABA binding sites per receptor. Benzodiazepines and the newer hypnotic drugs bind to allosteric sites on the receptor to potentiate GABA-mediated channel opening. Barbiturates act at a distinct allosteric site to also potentiate GABA inhibition (GABA-mimetic action). GABA is synthesized from glutamate (**Fig. 3.11**). Various drugs binding to GABA are described in **Fig. 3.12**.

Benzodiazepines and nonbenzodiazepines act as CNS depressants. Picrotoxin blocks the GABA-gated chloride channels. Loss of GABA-ergic transmission contributes to excessive excitability and can play an important role in the pathogenesis of a serious neurological disorder like epilepsy where the impulses spread uncontrollably.

Bicuculline too is a GABA receptor blocker that inhibits GABA\textsubscript{A} receptor function and is a potent convulsant. Both of these drugs are used experimentally to produce seizures in animals. Benzodiazepines and barbiturates increase GABA\textsubscript{A} receptor function (potentiate) and are

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**Fig. 3.11** Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system (CNS). It is synthesized from decarboxylation of glutamate, involved in regulating anxiety, which may be related to eating or sleep disorders.

**Fig. 3.12** Gamma-aminobutyric acid (GABA) receptors with its various ligands.
anticonvulsants. GABA₂ receptors are G-protein-coupled receptors (GPCRs) and largely presynaptic in location where they inhibit transmitter release. Baclofen, an agonist of GABA₂, is a muscle relaxant which is used as an antispastic drug.

**Glutamate**

Glutamate is a fast-acting excitatory neurotransmitter. This is the main excitatory neurotransmitter of the CNS. It is found in almost all CNS structures. Since this is a major neurotransmitter in the brain and spinal cord synapses, it is involved in almost all brain functions. Glutamate is synthesized within the brain from glucose (via KREBS cycle/α-ketoglutarate pathway in the body) and via glutamine (from glial cells in the brain). The actions of glutamate are terminated by uptake through excitatory amino acid transporters in the neurons and astrocytes. All agonists of glutamate stimulate receptors and increase excitation in the neuronal pathways. Behavioral effects vary depending on neural integration and the nature of the neurons activated. In high doses, all agonists induce seizures. Agonists and antagonists are listed in Box 3.6. Various glutamate receptors are given in Fig. 3.13.

**Glycine**

Glycine has a major role in the spinal cord, where it mediates inhibition of synaptic transmission. Glycine receptor is an ionotropic chloride channel analogous to the GABAₐ receptor. Strychnine, a competitive antagonist of glycine, removes spinal inhibition to skeletal muscle and induces a violent motor response. Glycine seems to be secreted by neurons in the lower brain stem at the same time as GABA.

**Peptides**

Endogenous opioids are peptides with analgesic properties which mediate “stress analgesia.” The examples include endorphins, enkephalins, dynorphins, etc. Apart from mediating stress analgesia, they are involved in regulation of pain for different brain areas. Also, the enhancement of flight or flight response is mediated via them. Some evidence suggests their linkage with memory via hippocampus and amygdale. Details are given in Table 3.4.

**Neuromodulators and Neurohormones**

Neuromodulators are fatlike substances which are water insoluble. Examples include cannabis or tetrahydrocannabinol (THC) and anandamide
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(after Sanskrit word = anandum). Another example is adenosine which is a nucleoside; sugar molecule bound with one of the two amino acids (purine or pyrimidine). This is involved in dilation of blood vessels, especially during sleep. Caffeine acts as an adenosine antagonist, which can cause headaches, drowsiness, and difficulty in concentrating. Caffeine can neutralize these effects.4

Neurohormones are not produced in the brain and work in various organ systems. Cholecystokinin, neuropeptide Y, substance P, thyroid hormone-releasing hormone, etc., are examples of the same. These are used in brain areas that control these organs.4

References

10. Kansas University Medical Centre. Available at: www.classes.kumc.edu/sah/resource. Last accessed April 3, 2021

Table 3.4 Major peptides and their functions

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance P</td>
<td>First peptide neurotransmitter discovered; role in pain</td>
</tr>
<tr>
<td>Gut hormones (gastrins)</td>
<td>Angiotensin, neuropeptide Y, cholecystokinin</td>
</tr>
<tr>
<td>Releasing factors</td>
<td>Thyrotropin, somatostatin, corticotrophin</td>
</tr>
<tr>
<td>Opiates</td>
<td>Encephalins, endorphins; pain pathways</td>
</tr>
<tr>
<td>Tachykinins</td>
<td>Substance K, substance P</td>
</tr>
<tr>
<td>Insulins</td>
<td>Insulin, insulinlike growth factors I and II</td>
</tr>
</tbody>
</table>