NEUROTRANSMITTERS, POSSIBLE SITES OF ACTIONS, AND DRUG INFLUENCES

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Abstract

Neurotransmitter, also known as chemical messengeris enodegenons chemical that enables neurotransmission. Neurotransmitters play a major role in shaping everyday life and function. There are criteria for identifying neurotransmitters. A neurotransmitter can influence the function of neuron through a remarkable number of mechanisms. Understanding the effects of drugs on neurotransmitters comprises a significant portion of research initiations in the field of neuroscience to ascertain ways neurotransmitter can effectively treat and someday possibly prevent or cure such illness.

Keywords: Neurotransmitters, Life, Functions, Mechanisms, Drugs, Research, Illness and Neuroscience.

Introduction

Neurotransmitter is a chemical substance that acts as the mediator for the transmission of nerve impulse from neuron to another neuron through a synapse. Existenceof neurotransmitter was first discovered by an Austrian scientist named Otto Loewi in 1921. He dreamt of an experiment, which he did practically and came out with this discovery. Nowadays, many substances are categorized as neurotransmitters. To consider a substance as a neurotransmitter, it should fulfill certain criteria as given below:

1. The substance must be found in a neuron
2. It must be produced by a neuron
3. It must be released by a neuron
4. After release, it must act on a target area andproduce some biological effect
5. After the action, it must be inactivated. (Sembulingam et al, 2000)

Classification of Neurotransmitters

- **Depending Upon Chemical Nature**

Many substances of different chemical nature are identifiedas neurotransmitters. Depending upon their chemical nature, neurotransmitters are classified into three groups

1. Amino Acids

The neurotransmitters of this group are involved in fast synaptic transmission and are inhibitory and excitatory in action. GABA, glycine, glutamate (glutamic acid) and aspartate (aspartic acid) belong to this group.

2. Amines

Amines are the modified amino acids. The neurotransmitters of this group involve in slow synaptic transmission. These neurotransmitters are also inhibitory and excitatory in action. Noradrenaline, adrenaline, dopamine, serotonin and histamine belong to this group.

3. Others

Some neurotransmitters do not fit into any of these categories. One such substance is acetylcholine. It is formed from the choline and acetyl coenzyme A in the presence of the enzyme

called cholineacetyltrans-ferase. Another substance included in this category is the soluble gas nitric oxide (NO).

- **Depending Upon Function**

Some of the neurotransmitters cause excitation of postsynaptic neuron while others cause inhibition. Thus, neurotransmitters are classified into two types:

1. Excitatory neurotransmitters
2. Inhibitory neurotransmitters

1. Excitatory Neurotransmitters

The excitatory neurotransmitter is the chemical substance which is responsible for the conduction of impulse from the presynaptic neuron. The neurotransmitter released from the postsynaptic axon terminal does not cause development of action potential in the postsynaptic neuron. Rather, it causes some change in the resting membrane potential slight depolarization by the opening of sodium channels in the postsynaptic membrane and the influx of sodium ions from ECF, The slight depolarization is called excitatory postsynaptic potential (EPSP). EPSP in turn causes development of action potential in the initial segment of the axon of the postsynaptic neuron. The common excitatory neurotransmitters are acetycholine and noradrenaline (Sara, 2008).

2. **Inhibitory Neurotransmitters**

The inhibitory neurotransmitter is the chemical sub-stance which inhibits the conduction of impulse from the presynatic neuron to the postsynaptic neuron. When it is released from the presynatptic axon terminal due to the arrival of action potential, it causes opening of potassium channels in the postsynaptic membrane and efflux of potassium ions. This leads to hyperpolization which is called the inhibitory postsynaptic potential (IPSP). When IPSP is developed, the action potential is not generated in the postsynaptic neuron. The common inhibitory neurotransmitters are gamma amino butyric acid (GABA) and dopamine. (Sembulingam et al, 2000)

Transport and Release of Neurotransmitter

The neurotransmitter is produced in the cell body neuron and is transported through the axon. At the axon terminal, the neurotransmitter is stored small packets called vesicles. Under the influence of a stimulus, these vesicles open and release the neurotransmitter into the synaptic cleft. It binds to specific receptors on the surface of the postsynaptic cell. The receptors are G proteins, protein kinase or ligand-gated receptors.

Inactivation of Neurotransmitters

After the execution of the action, neurotransmitter inactivated by four different mechanisms:

1. It diffuses out of synaptic cleft to the area where it has no action
2. It is destroyed or disintegrated by specific enzymes
3. It is engulfed and removed by astrocytes (macro-phages)
4. It is removed by means of reuptake into the axon terminal.

Reuptake of Neurotransmitter

Reuptake is a process by which the neurotransmitter is taken back from synaptic cleft into the axon terminal after execution of its action. The reuptake process involves a specific carrier protein for each neurotransmitter. Neurotransmitter are released into the synaptic cleft, they refuse until they reach the post synaptic membrane there; they bind to lonotropic or metabotropic receptors. The responses elicited by Neurotransmitters is determine by receptor to which it bunds

Two general families

lonotropic receptor gated on channels.

1. Linked to ion channels
2. activation results in post senaptic events that are rapid ones and decay Metaptropic Receptors

G-protein couple receptors

1. Activation result in modification of enzymes or membrane proton
2. Pest synaptic events have slower onset and longer duration.

Inotropic receptors

Two functional domains

1. Extracellular event binds neurotransmitters
2. membrane- spamming domain forms ion channel

Steps:

1. Neurotransmitters bind to receptors
2. Channel opens
3. Ion flow across membrane e.g. potassium, sodium, chloride and calcium

Examples of Inotropic receptors

1. Inotropic glutamate receptors
2. Inotropic GABA receptors
3. Nicotinic Ach Receptors

Metabotropic Receptors

Two functional domains

1. Extracellular domain binds neurotransmitters
2. Intracellular domain binds to G proteins

Note: G protein couple neurotransmitters binding to intracellular or membrane proteins.

Steps

1. Neurotransmitters binds receptors
2. G protein is activated
3. G protein subunits or intracellular messengers or second messengers modulation Ion channels
4. Ion channel opens
5. Ions flow across membrane

Examples of metabotropic receptors

1. Metabotropic glutamate receptors
2. Muscannic acetylcholine (Ach) receptors
3. Adrenergic receptors
4. GABA receptors
5. Most serotonin receptors
6. Histamine receptors
7. Endocarinabinods
8. Neuropeptides

A second messenger function is to activate other particles.

Functioned Difference between Ion Tropic and Metabolic Receptors

Ionotropic Receptors	Metabotropic Receptors
Act very quickly as soon as ligand binds to	Take a little longer to do anything depending on the number of steps, (second messenger) is required to

them, they change shape and allow ion to flow in, but the ligand doesn't stay in place very long, and the channel close back quickly.	produce response, but once activated, the second messenger can travel throughout the cell and result in much longer range of response.

Neurotransmitters and possible sites of action are given below:

Group	Name	Site of secretion	Action
Amino Acid	GABA	Cerebral cortex, cerebellum, basal ganglia, spinal cord and retina	Inhibitory
	Glycine	Forebrain, brainstem, spinal cord and retina	Inhibitory
	Glutamate	Cerebral cortex, brainstem, and cerebellum	Excitatory
	Aspartate	Cerebellum, spinal cord and retina	Excitatory
Amines	Noradrenaline	Postganglionic adrenergic sympathetic nerve endings, cerebral cortex, hypothalamus, basal ganglia, brainstem, locus ceruleus and spinal cord	Excitatory and Inhibitory
	Adrenaline	Hypothalamus, thalamus and spinal cord	Excitatory and Inhibitory
	Dopamine	Basal ganglia, hypothalamus, limbic system, neocortex, retina and sympathetic ganglia	Inhibitory
	Serotonin	Hypothalamus, limbic system, cerebellum, spinal cord, retina, Gl tract, lungs and platelets	Inhibitory
	Histamine	Hypothalamus, cerebral cortex, Gl tract and mast cells	Excitatory
others	Nitric oxide	Many parts of CNS, neuromuscular junction and Gl tract	Excitatory
	Acetylcholine	Preganglionic parasympathetic nerve endings Postganglionic parasympathetic nerve endings Preganglionic sympathetic nerve endings Postganglionic sympathetic cholinergic nerve endings Neuromuscular junction, cerebral cortex, hypothalamus, basal ganglia, thalamus, hippocampus and amacrine cells of retina	Excitatory

Sembulingam, et al (2000)

Excitatory neuro-transmitters	Inhibitory neuro-transmitters	Neurotransmitters with excitatory and inhibitory actions
1. Acetylcholine 2. Nitric oxide 3. Histamine 4. Glutamate 5. Aspartate	1. GABA 2. Glycine 3. Dopamine 4. Serotonin	1. Noradrenaline 2. Adrenaline

Sembulingam et al (2000)

NEUROTRANSMITTERS IN THE CENTRAL NERVOUS SYSTEM

Neurotransmitter	Location	Possible implications for mental illness
1. Cholinergics		
A. Acetycholine	**ANS**-Sympathetic and parasympathetic presynaptic nerve terminals: parasympathetic post-synaptic nerve terminals **CNS**- Cerebral cortex, hippocampus, limbic structures, and basal ganglia. **Functions:** Sleep, arousal, pain, perception, movement, memory	**Increased levels:** Depression **Decreased levels:** Alzheimer's disease, huntington's disease, parkinson's disease.
I. Monoamines		
A Norepinephrine	**ANS**- Sympathetic post-synaptic nerve terminals **CNS**- Thalamus, hypothalamus, limbic system, hippocampus, cerebellum, cerebral cortex. **Functions:** Mood, cognition, perception, locomotion, cardiovascular, functioning and sleep and arousal.	**Decreased levels:** Depression **Increased levels:** Mania, anxiety states, schizophrenia.

NEUROTRANSMITTERS IN THE CENTRAL NERVOUS SYSTEM ((contd...)

A. Dopamine	Frontal cortex, limbic system, basal ganglia, thalamus, posterior pituitary and spinal cord. **Functions:** Movement and coordination, emotions, voluntary judgment, release of prolactin.	**Decreased levels**: Parkinson's disease and depression **Increased levels:** Mania and schizophrenia.
A Serotonin	Hypothalamus, thalamus, limbic system, cerebral cortex, cerebellum, spinal cord **Function:** Sleep and arousal, libido, appetite, mood aggression, pain perception, coordination, judgment.	**Increased levels:** Anxiety states. **Decreased levels:** Depression
A. Histamine	Hypothalamus **Function:** Wakefulness, pain, sensation and inflammatory response	**Decreased levels:** Depression

Pharmacology and Neurotransmitters

Drugs can influence behavior by altering neurotransmitter activity. For instance, drugs can decrease the rate of synthesis of neurotransmitters by affecting the synthetic enzyme(s) for that neurotransmitter. When neurotransmitter syntheses are blocked, the amount of neurotransmitters available for release becomes substantially lower, resulting in a decrease in neurotransmitter activity. Some drugs block or stimulate the release of specific neurotransmitters. Alternatively, drugs can prevent neurotransmitter storage in synaptic vesicles by causing the synaptic vesicle membranes to leak. Drugs that prevent a neurotransmitter from binding to its receptor are called receptor antagonists. For example, drugs used to treat patients with schizophrenia such as haloperidol, chlorpromazine, and clozapine are antagonists at receptors in the brain for dopamine.

Other drugs act by binding to a receptor and mimicking the normal neurotransmitter. Such drugs are called receptor agonists. An example of a receptor agonist is Valium, a benzodiazepine that mimics effects of the endogenous neurotransmitter gamma-aminobutyric acid (GABA) to decrease anxiety. Other drugs interfere with the deactivation of a neurotransmitter after it has been released, thereby prolonging the action of a neurotransmitter. This can be accomplished by blocking re-uptake or inhibiting degradative enzymes.

Lastly, drugs can also prevent an action potential from occurring, blocking neuronal activity throughout the central and peripheral nervous system. Drugs such as tetrodotoxin that block neural activity are typically lethal.(Eyibe & Eyibe, 2015)

Drugs targeting the neurotransmitter of major systems affect the whole system, which can explain the complexity of action of some drugs. Cocaine, for example, blocks the re-uptake of dopamine back into the presynaptic neuron, leaving the neurotransmitter molecules in thesynaptic gap for an extended period of time. Since the dopamine remains in the synapse longer, the neurotransmitter continues to bind to the receptors on the postsynaptic neuron, eliciting a pleasurable emotional response. Physical addiction to cocaine may result from prolonged exposure to excess dopamine in the synapses, which leads to the down regulation of some post-synaptic receptors. After the effects of the drug wear off, an individual can become depressed due to decreased probability of the neurotransmitter binding to a receptor. Fluoxetine is a selective serotonin re-uptake inhibitor (SSRI), which blocks re-uptake of serotonin by the presynaptic cell which increases the amount of serotonin present at the synapse and furthermore allows it to remain there longer, providing potential for the effect of naturally released serotonin. AMPT prevents the conversion of tyrosine to L-DOPA, the precursor to dopamine; reserpine prevents dopamine storage within vesicles; and deprenyl inhibitsmonoamine oxidase (MAO)-B and thus increases dopamine levels. (Yadav, et al 2008 & Katzung, et al 2009)

Conclusion

There are approximately 50 neurotransmitters identified. There are billions of nerve cells located in the brain, which do not directly touch each other. Nerve cells communicate messages by secreting neurotransmitters. Neurotransmitters can excite or inhibit neurons (never cells). Some common neurotransmitters are acetylcholine , norepinephrine, dopamine, serotonin and gamma aminobutric acid (GABA). Acetycholine and noreipnephrine are excitatory neurotransmitters while dopamine, serotonin, and GABA are inhibitory. Each neurotransmitter can directly or indirectly influence neurons in a specific portion of the brain thereby affecting behaviour. The working principles of these neurotransmitters are useful in drugs production and treatment of health problems.

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