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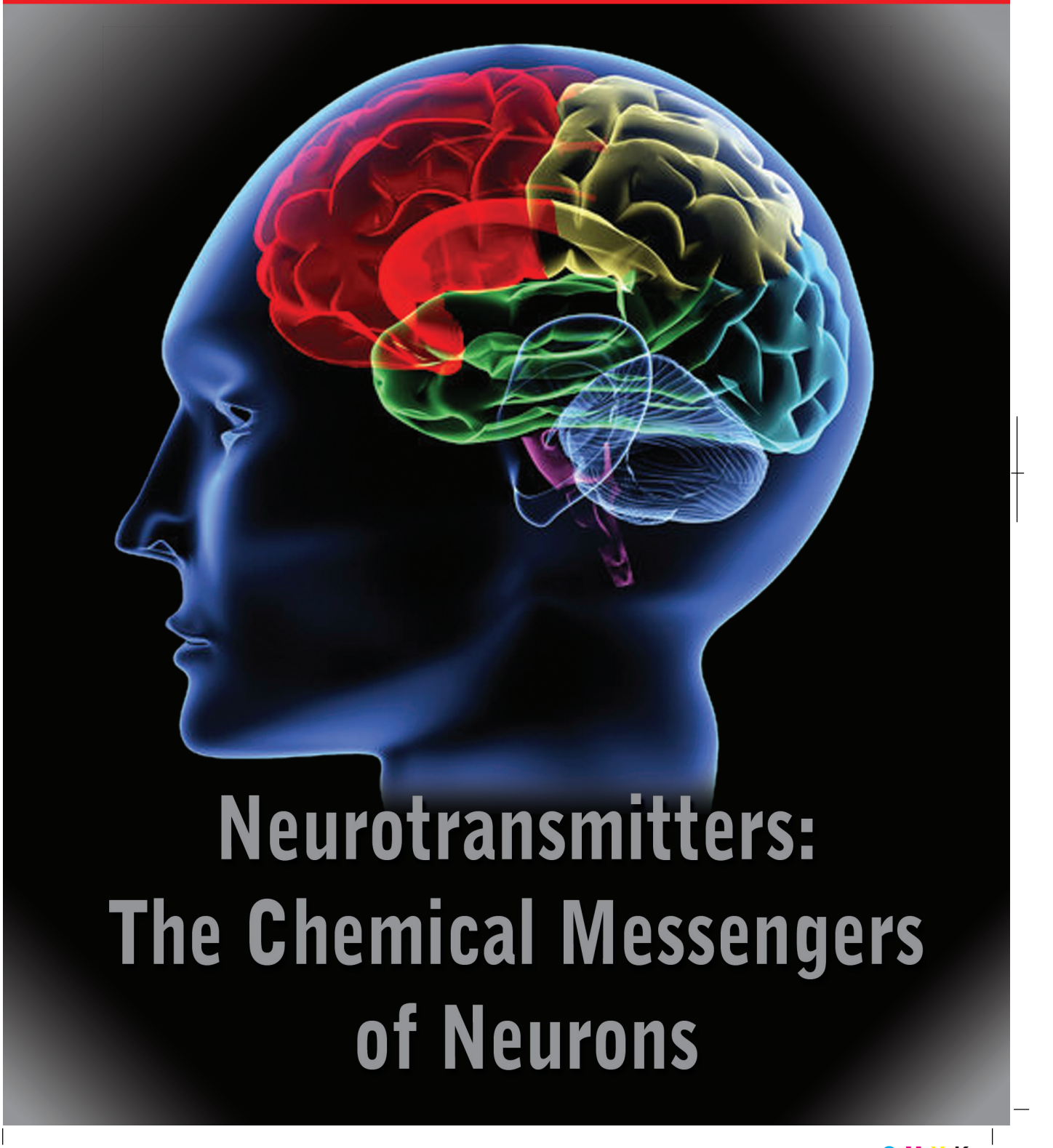

Neurotransmitters: The Chemical Messengers of Neurons

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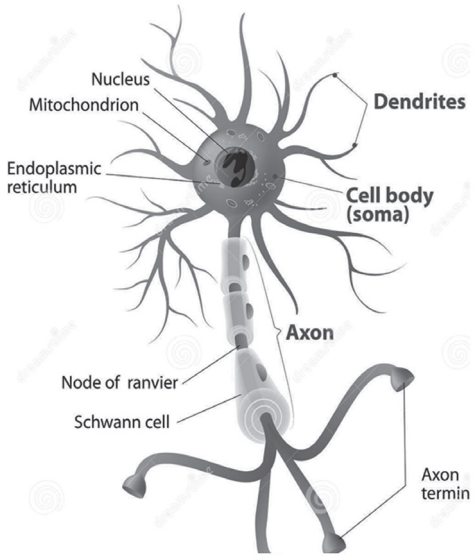
Neurotransmitters: The Chemical Messengers of Neurons

Prof. K.K. Mishra

Neurotransmitters are the chemical messengers responsible for communication between individual neurons. They have always been of great interest to neuroscientists. Neurotransmitters regulate the entire biological activities in human beings including even our mood, motivation and day to day behaviour. The present article is an attempt to give a generalized account of the chemistry of some important neurotransmitters.

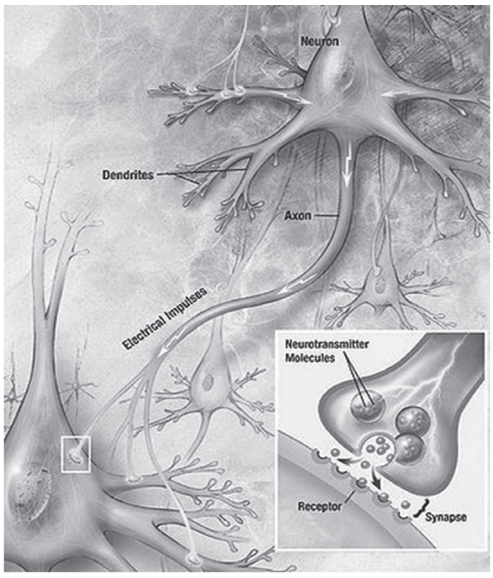
For a human being to think, act or merely to exist, the cells of the body must communicate with one another. They do so by means of two systems. One is hormonal system in which certain chemicals are released by endocrine glands directly into circulation and they convey the message to respective target cells. The other system of communication is nervous system in which electrical signals are generated in the form of nerve impulse which is usually associated with the rapid response to external stimuli. These two systems of communication in the body are not in isolation but they are very much integrated and inter-dependent in their functions. The nervous system is divided into the central nervous system (CNS) consisting of brain and spinal cord, and the peripheral nervous system (PNS) that includes all other nervous tissues. The CNS is further grouped into the ascending (to the brain) and descending (from the brain) pathways of neurons. Likewise, PNS is divided into afferent (Sensory) neurons which direct their information to CNS and efferent (Motor) neurons which direct their information away from CNS. The elementary structural unit of nervous system is the neuron, a nerve cell. The figure below shows the morphological



features of a typical neuron. A neuron possesses a cell body with numerous ramifications called dendrites, an axon and terminal fibres. The propagation of nerve impulse involves an alteration in the permeability of membrane that results in the free diffusion of Na^+ - K^+ ions. The impulse travels from dendrites to cell body and then down to terminal fibres *via*. axon. This impulse is relayed through the synapse – the specialized contact zone where one neuron communicates with another neuron.

The molecules that make the nervous system functionally dynamic are neurotransmitters. By definition a neurotransmitter is a chemical substance that is released synaptically by one neuron and subsequently affects another cell in a specific way.

Florey in 1962 coined the term neurotransmitter for a chemical which mediated synaptic transmission. According to Kendal and Schularz (1981), for a substance to be classified as a true neurotransmitter, four criteria must be satisfied. The chemical substance must be produced by the neuron, it must be released by the neuron in considerable amount to exert an effect on neighbouring neurons; exogenous application in appropriate amount must mimic the action of endogenously released compound; and a mechanism must exist to eliminate the neurotransmitter from the target tissue.



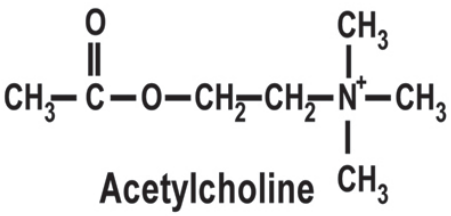
Communication between neurons

MONOAMINE TRANSMITTERS

Acetylcholine, histamine, serotonin, dopamine and norepinephrine are called as monoamine neurotransmitters since they all possess a single amino group in their structures.

Acetylcholine

Acetylcholine was the first substance to be identified as a neurotransmitter by Otto Loewi from Germany in 1921. He demonstrated the release of acetylcholine from the vagus nerve in a frog through a well set experiment. Stimulation of the nerve stopped the heartbeat. Loewi perfused the region with a physiological solution, removed the solution and employed it to another frog heart. The second heart also stopped beating. Subsequently, acetylcholine was extracted



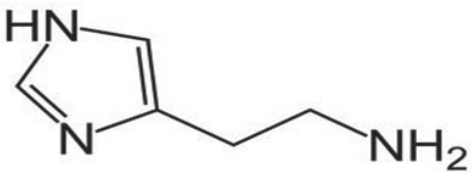
Acetylcholine

from the solution and identified as a chemical mediator. The synthesis of acetylcholine occurs in the cell body of the neuron. The enzyme choline acetyltransferase catalyzes the reaction between acetyl CoA and choline.

Acetylcholine is a transmitter of motor neurons in the spinal cord and is the transmitter at all of the nerve skeletal muscle junctions in vertebrates. Systems that use acetylcholine as a neurotransmitter are called cholinergic systems. Acetylcholine released from pre-synaptic membrane is poured into the synaptic cleft. Its action on post-synaptic membrane involves binding with a receptor protein and an alteration in the permeability of membrane occurs. A number of researchers have reported that patients with Alzheimer's disease have significantly lower concentration of enzyme choline acetyltransferase in their brains. To date, two types of acetylcholine receptors have been identified such as nicotinic receptors and muscarinic receptors, after their respective agonists. Biochemical response to these two receptors is quite different. One of the biochemical responses is the elevation of cyclic guanosine triphosphate (cGTP) as a result of increased guanylyl cyclase. The elimination of acetylcholine from post-synaptic neurons takes place by hydrolysis to choline and acetate by acetylcholine transferase enzyme.

Histamine

Histamine is synthesized from the essential amino acid L-histidine by a decarboxylation reaction. There are two

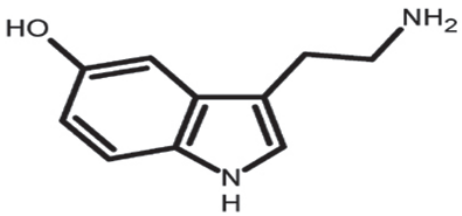


Histamine

kinds of histamine receptors designated as H_1 and H_2 receptors. Upon its binding to these receptors, adenylyl cyclase is activated and an increase in concentration of adenosine 3', 5'-cyclic monophosphate (cAMP) results in the intracellular fluid. Binding of histamine to H_1 receptor also results in increase in cyclic GTP levels. Histamine plays a central role in such neural responses as thirst, antidiuresis and hypothermia.

Serotonin

Serotonin is chemically 5-hydroxy tryptamine. It is a classical neurotransmitter which is synthesized from an amino acid called tryptophan. Insomnia, depression, psychosis are the result of serotonin function and related disturbances. Distributed in the various regions of the brain, it mediates the sensation of pain, right down through the spinal cord. Serotonin makes us aware of day and night and regulates sleep-wake mechanism.



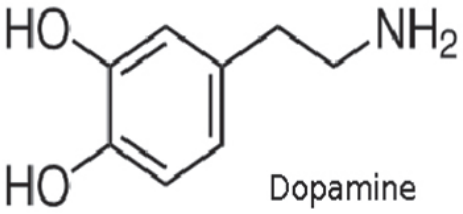
5-hydroxy tryptamine (Serotonin)

It is really a matter of great surprize that the most potent hallucinogen Lysergic acid

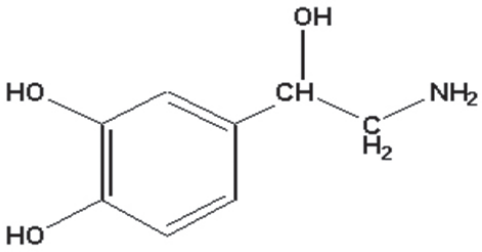
Diethylamide (LSD) derived from *Claviceps purpurea*, a fungus, has a good structural similarity with serotonin molecule. Three types of serotonin receptors have been identified. One is inhibitory, that is when serotonin binds to this receptors, inhibition of nerve impulse relay or related metabolic changes occurs. The second type of receptor called autoreceptor involves the mediation of the response of neuron to its own neuroreceptors. The third, an excitatory receptor is the type which causes propagation of an impulse. Serotonin is eliminated from the synaptic cleft, by degradation into 5-hydroxyindole acetic acid in the presence of the enzyme monoamine oxidase.

Catecholamines

Catecholamines are a group of compounds having a common catechol structure. Dopamine and norepinephrine are referred to as catecholamines. The first definite evidence for neurochemical transmission for catecholamines was observed by Otto Loewi. However, it was not until 1946 when Ulf Von Euler succeeded in identifying and isolating norepinephrine as neurotransmitter in sympathetic nervous system. Dopamine and norepinephrine are synthesized through a common pathway. Tyrosine is converted into L 3', 4'–dihydroxy phenylalanine (L-DOPA) by tyrosine



Dopamine

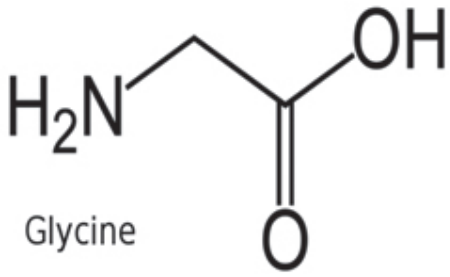


Norepinephrine

hydroxylase. This is the rate determining step in the synthesis of catecholamines. Dopamine plays a cardinal role in the elicitation of certain behaviour such as locomotor activity, hunger and satiety together with thermoregulation. Dopaminergic systems have been related to Parkinsonism and Schizophrenia. The regions of CNS affected by these disorders contain high concentrations of dopamine neurons and are found in the brainstem, midbrain and hypothalamus. The two major types of receptors for norepinephrine are the alpha and beta adrenergic receptors. Alpha adrenergic receptor-mediated responses are found in smooth muscle contraction and beta adrenergic receptors play roles in such responses as ionotopism in heart tissue. Binding of the norepinephrine with receptor has been shown to affect cAMP metabolism in post-synaptic cell. Catecholamines are eliminated by getting metabolized in the presence of enzyme monoamine oxidase.

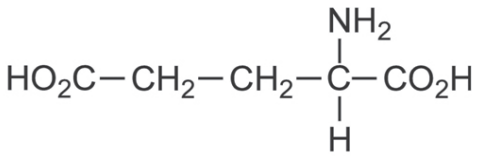
AMINO ACID TRANSMITTERS

Glycine, L-glutamic acid and gamma-amino butyric acid (GABA) are well known examples of classical neurotransmitters. Glycine, chemically an amino acetic acid, is the simplest essential amino acid. It is



Glycine

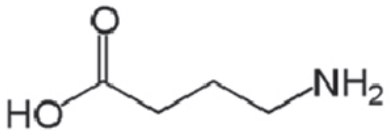
an inhibitory transmitter of the spinal cord inter-neurons. Comparatively, much is not known about glycine systems. Glycine may be formed from serine by methylation with tetrahydrofolate. L-glutamic acid and GABA are the major workhouse neurotransmitters of brain. It is known to be an excitatory neurotransmitter. Glutamic acid is one of the 20-22 proteinogenic amino acids and its codons are GAA and GAG. It is a non-essential amino acid with a side chain carboxylic acid functional group. The carboxylate anions and salts of glutamic acid are known as glutamates. It is the most common neurotransmitter in the central nervous system - as much as half of all neurons in the brain - and it plays an important role with regard to memory. Curiously, glutamate is actually toxic to neurons and an excess will prove fatal.



L - glutamic acid

Glutamate was discovered more than a century ago by Kikunae Ikeda of Tokyo Imperial University in 1907 while looking for flavour common to things like cheese, meat and mushrooms. He extracted an acid from seaweed, the glutamate. He went on to invent monosodium glutamate (MSG) which is used as a flavouring agent or taste enhancer in foods and beverages. But it took decades for Peter Usherwood to identify glutamate as a neurotransmitter in 1994.

Of amino acid transmitters, GABA is the most studied and fascinating neurotransmitter. Though its existence was reported in brain in 1950, a final confirmation of GABA being a legitimate neurotransmitter came only in 1970. It is formed from glutamic acid through a decarboxylation reaction. In patients of anxiety-neurosis and depression, the levels of GABA and its functional efficacy in CNS is reported to be diminished. The most widely employed anxiolytic drug Diazepam is supposed to be acting by enhancing the effectiveness of GABArgic system.



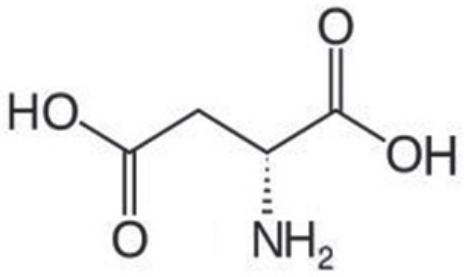
Gamma-aminobutyric acid (GABA)

RECENT RESEARCHES IN NEUROCHEMISTRY

In the past few decades, there has been an outburst of knowledge in neurochemistry. The identification of ATP, a form of cellular energy as a significant neurotransmitter and investigation of neuronal action of nitric oxide (NO) have opened new avenues for further extensive research in this field. The discovery that ATP is a neurotransmitter by Geoffrey Burnstock in 1980 was not only ignored but ridiculed also. But recent studies have finally provided requisite evidences to

prove that ATP is indeed a major neurotransmitter. One could hardly imagine a decade ago that NO is a highly significant regulator involved in higher organisms. The story began in the early 1980s in different areas of biochemical research. The most startling and relatively recent aspect of NO is its involvement in brain functions. The researchers are surprised at the unusual action of NO. Unlike other transmitters, it is toxic and is not stored in vesicles, rather produced on demand. Nitric oxide is synthesized from the semi-essential amino acid L-arginine by NO Synthase. The precise biosynthetic pathway is still not very clear but hydroxy arginine is an intermediate. Nitric oxide is a central and peripheral neuronal messenger. It is involved in classical anterograde neuronal signalling and has also unique properties as a retrograde transmitter. Within the CNS, nitric oxide is released in response to increase in intracellular Ca^{2+} that follow stimulation of glutamate receptors. Immuno-histochemical studies have shown that Ca^{2+} Calmodulin-dependent NO Synthase is distributed in discrete areas throughout the brain with high concentrations in cerebellum, hippocampus and olfactory lobe.

Of late a team of scientists has discovered that D-aspartic acid (D-Asp) is a novel neurotransmitter that could potentially be used in the fight against neurological diseases such as Parkinson's and Schizophrenia. D-Asp meets all of the criteria that characterize biological molecules which exhibit neurotransmitter activity: they are present in high



D-Aspartic Acid

concentrations in the synaptic vesicles of axon terminals; synthesis for this amino acid occurs in neurons by conversion of L-Asp to D-Asp *via*. D-aspartate racemase; depolarization of nerve endings with potassium ions evokes an immediate release of D-Asp in a Ca^{2+} dependent manner; specific receptors for D-Asp occur at the post-synaptic membrane; and stimulation of nerve endings with D-Asp triggers signal transduction by increasing the second messenger cAMP. D-Asp plays an important role in the initial phases of central nervous system development in vertebrates and invertebrates. In humans, mice and chicken, large quantities of this molecule are produced in the brain during embryonic development.

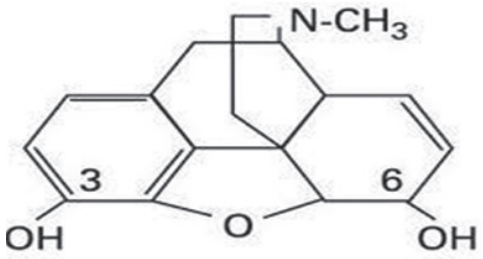
After birth, D-Asp falls to minute levels and remains constant throughout the adult stage life. Evidence suggests that the molecule is involved in the learning process and memory function in rats and enhances the cognitive capabilities of animals in a range of experiments. According to Professor Jordi García-Fernàndez, "Basic research leads to advances in applied work by describing new functional mechanisms that explain

the complex biological machinery of the nervous system". This study is of particular interest in the field of dementia, as it describes a novel neurotransmitter with a potential use in the treatment of certain neurological diseases such as Parkinson's disease and Schizophrenia.

Endorphin

In 1973, Solomon Snyder and Candace Pert of Johns Hopkins University discovered endorphin. Endorphin is short for "endogenous morphine." It is structurally very similar to the opioids (opium, morphine, heroin, etc.) in their abilities to produce a feeling of well-being and has similar functions. It is involved in pain reduction and pleasure, and the opioid drugs work by attaching to endorphin's receptor sites. They are produced by the brain during exercise, excitement, consumption of certain foods, love and orgasm.

β -Endorphin is an endogenous opioid neuropeptide found in the neurons of both the central and peripheral nervous system. β-Endorphin is a peptide, 31 amino acids long. It is found in neurons of the hypothalamus, as well as the pituitary gland. β-Endorphin was discovered by Li and Chung in 1976. It is one of the five endorphins found in humans, the others are- alpha endorphin, gamma endorphin, alpha neoendorphin and beta neoendorphin. It is used as an analgesic in the body to numb for dull pains. That is the reason why humans start to feel better immediately after an acute physical trauma even though the symptoms are still present. It is because of body's own



Morphine

response to trauma in order to control the sensation of pain. The reason the pain dulls is because it binds to and activates opioid receptors. Beta endorphin is a very potent analgesic, and is approximately 18-33 times more powerful than morphine, a natural pain killer.

The search for novel neurotransmitters is far from over. There are several potential candidates in queue waiting to compete and qualify. Researchers suggest that it is very likely that there are many weird chemicals which are neurotransmitters of future.

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