NEUROTRANSMITTERS AND MODULATORS

Simo S. Oja and Pirjo Saransaari
The Centre for Laboratory Medicine, Tampere University Hospital, Finland

Keywords: Synapses; nerve impulses, neurotransmission, neuromodulation, synaptic receptors.

Contents

1. Introduction
2. Acetylcholine
3. Synthesis and Breakdown of Amine Transmitters
4. Dopamine
5. 5-Hydroxytryptamine
6. Histamine
7. Purine Transmitters
8. Synthesis, Breakdown and Transport of Amino Acid Transmitters
9. Glutamate
9.1. Ionotropic Glutamate Receptors
9.2. Metabotropic Glutamate Receptors
9.3. Glutamate Receptors and Neuronal Damage
10. \(\gamma\)-Aminobutyrate (GABA)
10.1. GABA\(_A\) Receptors
10.2. GABA\(_B\) Receptors
11. Glycine
12. Peptide Transmitters and Modulators
13. Nitric Oxide and Carbon Monoxide
Glossary
Bibliography
Biographical Sketches

Summary

The majority of functional connections of nerve cells are chemical synapses in which information molecules transmit nerve impulses from cell to cell. This chapter overviews the compounds which are known or assumed to function as neurotransmitters. The synthesis, transport and breakdown of these compounds, the nature and properties of their specific receptors, and the sequences of the receptor activation are discussed in some detail. Neuromodulation and co-transmission are briefly considered as well.

1. Introduction

Neurotransmitter and -modulators are the basic working tools in the transfer of information from a neurone to a neurone. They also apparently function in this propensity between neurones and glial cells (see Neurones, Action Potentials and Synapses). There are a great number of recognized neurotransmitters (Table 1). They can be divided in different categories as follows: (1) acetylcholine, catecholamines,
histamine and 5-hydroxytryptamine (serotonin), and purines (2) amino acid transmitters, (3) peptides, and (4) unorthodox transmitters, such as nitric oxide and possibly carbon monoxide. Neuropeptides mostly do not act as pure transmitters but rather as neuromodulators controlling the activity of several types of receptors.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Examples of principal locations of occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>Throughout brain, neuromuscular junctions, autonomic preganglionic terminals</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Striatum, cerebral frontal cortex, limbic system, hypothalamus</td>
</tr>
<tr>
<td>Norepineprine</td>
<td>Several brain regions, sympathetic postganglionic terminals</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Thalamus and hypothalamus</td>
</tr>
<tr>
<td>5-HT</td>
<td>Limbic system, hypothalamus</td>
</tr>
<tr>
<td>Histamine</td>
<td>Hypothalamus</td>
</tr>
<tr>
<td>Adenosine</td>
<td>Hippocampus, cerebral cortex, cerebellum</td>
</tr>
<tr>
<td>ATP</td>
<td>Habenula, autonomic ganglia</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Throughout brain and spinal cord</td>
</tr>
<tr>
<td>Aspartate</td>
<td>Spinal cord</td>
</tr>
<tr>
<td>Glycine</td>
<td>Medulla and spinal cord</td>
</tr>
<tr>
<td>GABA</td>
<td>Throughout brain and spinal cord</td>
</tr>
<tr>
<td>Substance P</td>
<td>Many parts of brain, nociceptive tracts</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>Several brain parts, substantia gelatinosa</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Posterior pituitary gland, medulla and spinal cord</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>Posterior pituitary gland, medulla and spinal cord</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Nociceptive pathways</td>
</tr>
<tr>
<td>Neurotensin</td>
<td>Hypothalamus</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>Hypothalamus, amygdala, spinal cord</td>
</tr>
<tr>
<td>VIP</td>
<td>Hypothalamus, cerebral cortex, parasympathetic postganglionic neurones</td>
</tr>
<tr>
<td>CCK</td>
<td>Hypothalamus and cerebral cortex</td>
</tr>
<tr>
<td>Gastrin</td>
<td>Hypothalamus and medulla</td>
</tr>
<tr>
<td>Galanin</td>
<td>Hypothalamus and hippocampus</td>
</tr>
<tr>
<td>CGRP</td>
<td>Medial forebrain bundle, taste pathways</td>
</tr>
<tr>
<td>Neuropeptide Y</td>
<td>Hypothalamus and other brain regions</td>
</tr>
<tr>
<td>Glutathione</td>
<td>Throughout brain</td>
</tr>
<tr>
<td>NO</td>
<td>Throughout brain</td>
</tr>
<tr>
<td>CO</td>
<td>Several brain regions</td>
</tr>
</tbody>
</table>

The above list is not exhaustive since more than 50 short peptides have been shown to be pharmacologically active in nerve cells. On the other hand, the transmitter function
of some of the above peptides has not been unequivocally proved. See the text for the full names of the compounds listed as abbreviations.

Table 1. Neurotransmitters and modulators in the mammalian central nervous system.

2. Acetylcholine

The history of acetylcholine (ACh) as a mediator of cellular communication is already almost one hundred years long. ACh is synthesized in the soma of cholinergic neurones by choline acetylase from its immediate precursors, choline and acetyl coenzyme A (Figure 1). Most of ACh in the brain is located in nerve endings but some is also detectable in axons on its way from the soma. The high-affinity uptake system of choline seems to be the rate-limiting step in ACh synthesis, even though cholinergic neurones possess a high-affinity uptake system for choline. Another high-affinity transport system concentrates ACh in the synaptic vesicles. The transporter (VAChT) is already cloned and expressed. A selective inhibitor of VAChT, vesamicol inhibits the vesicular uptake of ACh and also blocks the release of newly synthesized ACh, corroborating thus the assumption that vesicles are the sites of ACh release. The acetylcholine released into synaptic clefts is very rapidly degraded by acetylcholine esterase, which ends in this manner the transmitter action of ACh (Figure 2). In addition to the specific acetylcholine esterase, other acetylcholine esterases, so-called pseudocholine esterases, are widely distributed in the organism. A number of acetylcholine esterase inhibitors are currently used as drugs in clinical practice and some others are powerful insecticides.

![Figure 1. Synthesis and breakdown of acetylcholine (ACh).](image)

Initially ACh was found to mimic the responses to parasympathetic nervous stimulation in the heart. Soon it became evident that there are distinct different forms of ACh receptors, which explained the differing responses obtained in different experimental set-ups and test preparations. The initial typing of ACh receptors was pharmacologically based on the effects of two alkaloids, nicotine and muscarine. Atropine was discovered to be an antagonist of the muscarinic type of receptors and d-tubocurarine an antagonist of the nicotinic type. The nicotinic receptor was also the first transmitter receptor
purified. Subsequently, the existence of several nicotinic and muscarinic receptors was ascertained. The mature neuronal nicotinic ACh receptor consists of five subunits, two identical \( \alpha \) subunits, and one of each \( \beta, \gamma, \) and \( \delta \) subunits, arranged in a nearly symmetric fashion though the cell membrane and surrounding the central ion channel. The binding of ACh to the receptors opens the channel allowing the passage of Na\(^+\) and other cations, the neuronal nicotinic receptors being prominently permeable to Ca\(^{2+}\). At present, molecular biology studies through cloning by recombinant deoxyribonucleic acid (DNA) techniques have shown the existence of at least eight sequences of \( \alpha \) subunits and three sequences of \( \beta \) subunits in nicotinic receptors. The receptors with different subunit combinations endow them the ability to exhibit different sensitivities toward various agonists and antagonists—a phenomenon also commonly shared by other receptor classes.

![Figure 2. Turnover of acetylcholine (ACh) in the synaptic region.](image)

ACh released from storage vesicles into the synaptic cleft diffuses to its postsynaptic receptors and is then rapidly hydrolyzed by membrane-bound acetylcholine esterase to choline and acetate. The former is taken up into the synaptic terminal by means of choline transporter. Choline molecules are reincorporated into acetylcholine in a reaction catalysed by choline acetylase. The resynthesized acetylcholine is transported back into synaptic vesicles for further use.
In the above manner, the existence of five genes encoding five muscarinic receptors, M1-M5, has been demonstrated. The muscarinic receptor has the ligand recognition site within the outer half of the membrane-embedded part of the receptor glycoprotein and seven membrane-spanning α-helical domains. The C-terminus is on the intracellular side of the membrane. The receptors are coupled through guanosine triphosphate (GTP)-binding proteins (G-proteins) with several intracellular messenger systems—phospholipase C (PLC), protein kinase C (PKC), inositol-1,4,5-triphosphate (IP3), diacylglycerol (DAG) and Ca2+—the actions depending on the receptor type. In this manner the receptors secondarily affect the functions of plasma membrane K+ and Ca2+ channels. Muscarinic receptors are widespread in the central nervous system but nicotinic receptors are scant in the brain. Nicotinic receptors are located predominantly in peripheral ganglia and at neuromuscular junctions in the skeletal muscles. On the other hand, postganglionic parasympathetic transmission is mediated by muscarinic receptors. The muscarinic receptors in the central nervous system are involved in motor control, temperature regulation, cardiovascular regulation and memory. Ach is the endogenous agonist of both muscarinic and nicotinic receptors.

3. Synthesis and Breakdown of Amine Transmitters

The catecholamine transmitters, dopamine, norepinephrine and epinephrine, are synthesized from the aromatic amino acid tyrosine (Figure 3). Serotonin (5-hydroxytryptamine, 5-HT) is formed from the indole amino acid tryptophan (Figure 4) and histamine from the imidazole amino acid histidine (Figure 5). They are traditionally, though chemically imprecisely, collectively designated as biogenic amines. The first step in five consecutive enzyme reactions, tyrosine hydroxylation, is rate-limiting for the synthesis of dopamine and norepinephrine. In this hydroxylation reaction L-dihydroxyphenylalanine (L-DOPA) is formed (Figure 3). In neurology, L-DOPA is extensively used as a drug in treatment of Parkinsonian patients to compensate for the irreversible loss of dopaminergic nigrostriatal neurons. L-DOPA is decarboxylated by the aromatic L-amino acid decarboxylase to dopamine which is further converted to norepinephrine by dopamine β-hydroxylase and finally to epinephrine by the fifth enzyme phenylethanolamine-N-methyl transferase. The presence of these enzymes determines at which step the synthesis stops and which catecholamine transmitter is used in a certain neurone. Of the above enzymes, dopamine β-hydroxylase is tightly bound to the inner surface of aminergic vesicles in nerve endings. Norepinephrine is apparently the only transmitter synthesized within the vesicles. The production of norepinephrine in nerve cells is highly regulated to meet wide variations in neuronal activity. In the few adrenergic neurones in the brain and in the adrenal medullary cells in which epinephrine is formed, norepinephrine first leaves the synaptic vesicles to be methylated by the cytoplasmic enzyme and then taken up again into vesicles.

In the synthesis of 5-HT, tryptophan is first hydroxylated to 5-hydroxytryptophan which is then decarboxylated to 5-HT (Figure 4). As in the synthesis of catecholamines, the first hydroxylation step is rate-limiting. Normally, the hydroxylase is not saturated by tryptophan. Therefore, an increased dietary supply of tryptophan can increase the 5-HT synthesis and content in the brain. Histamine is formed through a direct decarboxylation from its immediate precursor histidine (Figure 5). The decarboxylase appears to be
characteristic of histaminergic neurones and specific for histidine, differing from the above aromatic L-amino acid decarboxylase.

Figure 3. Synthesis of catecholamine transmitters dopamine, norepinephrine and epinephrine.

Figure 4. Synthesis of 5-hydroxytryptamine (5-HT)
Dopamine is metabolized to inactive metabolites, 3,4-dihydroxyphenylacetate (DOPAC) and 3-methoxytyramine, by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT), respectively. The former metabolite is methylated by COMT and the latter oxidatively deaminated by MAO to yield in both cases another important metabolite, homovanillate (HVA). The rates of formation of DOPAC and HVA are generally used as indicators of the rate of dopamine breakdown, providing in this manner an insight into the turnover of dopamine in the brain. The catabolism of epinephrine and norepinephrine mimic that of dopamine. Both COMT and MAO participate in their breakdown. MAO and COMT are widely distributed throughout the body, but in nerve endings MAO is the enzyme responsible for the breakdown synaptic catecholamines due to the absence of COMT from these organelles. Consequently, the primary breakdown product of synaptic norepinephrine is 3,4-dihydroxymandelic aldehyde that is then readily converted to 3,4-dihydroxymandelate and 3,4-dihydroxyphenylglycol. The most part of hormonal epinephrine and norepinephrine is O-methylated by COMT, however, and the rates of O-methyl derivatives can be used as indicators of the peripheral secretion of epinephrine and norepinephrine. 5-HT is inactivated by MAO to form 5-hydroxyindoleacetate (5-HIAA), and its appearance is used as an indicator of 5-HT metabolism. Two isozymes of MAO, MAO-A and MAO-B, have been identified. MAO-A preferentially deaminates norepinephrine and 5-HT, whereas MAO-B shows a wide spectrum of activity towards phenylethylamines. At present, MAO-B inhibitors are used as adjuncts together with L-DOPA to treat Parkinsonism or as monotherapy in mild cases during the early course of the disease. There are again two pathways for the catabolism of histamine, either oxidative deamination by diamine oxidase (histaminase) to imidazoleacetate or N-methylation by histamine-N-methyltransferase to methylhistamine that is then oxidised by MAO to methylimidazoleacetate. All the above metabolites of these strongly neurally active amines are biologically inactive.

The cytosolic concentrations of catecholamines are normally very low, since catecholamines are rapidly degraded by MAO. After the cytosolic steps of synthesis, dopamine and the norepinephrine precursor are vividly taken up into the storage vesicles in which the concentration of catecholamines is of the order of 0.5 M. The cloned vesicular amine transporters have been shown to possess apparently 12
transmembrane domains. The vesicular uptake can be blocked by reserpine since the vesicular transporter (VMAT2) has a high affinity for this drug which profoundly depletes endogenous catecholamines in vivo. Normally, efficient regulatory mechanisms tend to keep the catecholamine contents in nerve endings relatively constant in spite of marked changes in the activity of neurones. Catecholamines released into synaptic clefts after impinging stimulation are taken up into the nerve endings. The saturable uptake conforming Michaelis kinetics is mediated by transporters located in neuronal plasma membranes. The cloned norepinephrine and dopamine transporters seem to be separate entities with 11 to 13 transmembrane domains but belonging to the large family of neurotransporters. One part of the catecholamines taken up is then degraded in the cytosol but a major part is accumulated into synaptic vesicles for future reuse.

4. Dopamine

Initially, two dopamine receptors (D1 and D2) were identified. The former were shown to stimulate and the latter to inhibit adenylyl cyclase. Recently, several subtypes have been characterized and their amino acid sequences determined. Subtypes D1 and D5 exhibit the original D1-like activity and subtypes D2S/D2L, D3 and D4 the D2-like activity. All identified dopamine receptors are thus coupled to G-proteins. They contain seven hydrophobic domains, an intracellular C-terminus and an extracellular N-terminus. The distribution of different dopamine subtypes varies within the brain and their sensitivity to drugs and affinity for dopamine is not similar. Over-activation of dopamine receptors has been implicated in psychotic disorders and the efficacy of antipsychotic drugs thought to be mediated through their antagonism at these receptors.

TO ACCESS ALL THE 23 PAGES OF THIS CHAPTER,
Visit: [http://www.eolss.net/Eolss-sampleAllChapter.aspx](http://www.eolss.net/Eolss-sampleAllChapter.aspx)

Bibliography


Cherubini E. and Conti F. (2001). Generating diversity at GABAergic synapses. Trends in Neuroscience 24, 156-162. [How can the GABAergic neurotransmitter system generate so diverse physiological effects and show differing responses to pharmacological agents?]


Sealfon S.C. and Oleanow C.W. (2000). Dopamine receptors: from structure to behavior. Trends in Neuroscience 23 (10 suppl), S34-S40. [A review on dopamine receptors and an evaluation of their behavioural influences.]


Biographical Sketches

Simo S. Oja, MD, MScD, PhD, ML, Professor in Biomedical Sciences (physiology), University of Tampere, Director of Tampere Brain Research Center, and Docent in Biochemistry, University of Oulu, Finland.

Born in 1939 in Kärkölä, Finland. Master of Science (MSc) 1962, Medical Doctor (MD) 1964, Licentiate in Philosophy (PhL) 1965, Doctor of Philosophy (PhD) 1966, Doctor of Medical Sciences (MScD) 1967 (all in University of Helsinki), and Master of Civil and Criminal Law (ML) 1988 (University of Turku).

Research Associate in Biochemistry 1960 (University of Helsinki), Research Associate in Physiology 1961-1963 (University of Helsinki), Postdoctoral Fellow in Physiology and Biophysics 1963 (University of Kentucky, KY, USA) Research Associate and Junior Research Fellow 1964-1966 (Academy of Finland, Medical Research Council), Associate Professor in Biochemistry 1966-1971 (University of Oulu), Senior Research Fellow 1971-1972 (Academy of Finland, Research Council for Sciences), Docent in Biochemistry since 1971 (University of Oulu), Professor in Biomedical Sciences (medical biochemistry) 1972 (University of Tampere), Professor in Biomedical Sciences (physiology) since 1973 (University of Tampere), and Director of Brain Research Center since 1990 (University of Tampere).

Pirjo Saransaari, PhD, Professor in Physiology, University of Tampere, Finland.

Born in 1944 in Tampere, Finland, MSc 1967 (University of Helsinki), and PhD 1980 (University of Oulu). Docent in Neurochemistry 1981 (University of Tampere) and Docent in Physiology 1986 (University of Tampere). Assistant and Senior Assistant in Biomedical Sciences 1972-1982, Research Associate, Junior Research Fellow and Senior Research Fellow 1977-1987 (Academy of Finland, Medical Research Council), Senior Assistant in Physiology 1983-1995 (University of Tampere), Associate Professor in Physiology 1996-1997 (University of Tampere), Professor in Medical Biochemistry 1997-1998 (University of Tampere), Senior Scientist 1992-1993 and 1999-1999 (Academy of Finland, Councils of Natural Sciences and Health Science), and Professor in Physiology since 1999 (University of Tampere).